2014-1391

IN THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

PAR PHARMACEUTICAL, INC.,
ALKERMES PHARMA IRELAND LIMITED,

Plaintiffs-Appellants,

v.

TWI PHARMACEUTICALS, INC.,
TWI PHARMACEUTICALS HOLDING, INC.,

Defendant-Appellee.

Appeals from the United States District Court for the District of Maryland in Case No. 1:11-cv-02466-CCB, Judge Catherine C. Blake

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CERTIFICATE OF INTEREST

Counsel for Plaintiff-Appellant Par Pharmaceutical, Inc. certifies the following:

1. The full name of every party or amicus curiae represented by me is:

   Par Pharmaceutical, Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

   N/A

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

   Par Pharmaceutical, Inc., a nongovernmental corporate entity, is a wholly-owned subsidiary of Par Pharmaceutical Companies, Inc. Par Pharmaceutical Companies, Inc. is a wholly-owned subsidiary of Sky Growth Holdings Corporation, which has no parent corporation, and no publicly held company owns 10% or more of the stock of Sky Growth Holdings Corporation.

4. The names of all law firms and the partners or associates that appeared for the party or amicus curiae now represented by me in the trial court or agency or are expected to appear in this court are:

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1. The full name of the party represented by us is: Alkermes Pharma Ireland Limited.

2. The name of the real party in interest represented by us is: not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party represented by us are: Alkermes Pharma Ireland Limited is a subsidiary of Alkermes plc, a publicly held corporation. FMR LLC; Wellington Management Company, LLP; and T. Rowe Price Associates, Inc. all own 10 percent or more of Alkermes plc's stock.

4. The names of all law firms and the partners or associates that appeared for the party represented by us in the trial court or are expected to appear in this Court are:

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STATEMENT OF RELATED CASES

The following case is pending in district court and could potentially be affected by this appeal: *Par Pharmaceutical, Inc. and Alkermes Pharma Ireland Ltd. v. Breckenridge Pharmaceutical, Inc.*, No. 1:13-cv-01114 (Robinson) (D. Del.).

JURISDICTIONAL STATEMENT

Under Federal Rule of Appellate Procedure 28(a)(4) and Federal Circuit Rule 28(a)(5), counsel for Par Pharmaceutical, Inc. and Alkermes Pharma Ireland Limited (collectively, "Par") state:

(a) The U.S. District Court for the District of Maryland had subject matter jurisdiction over this patent-infringement suit under 28 U.S.C. §§ 1331 and 1338(a).

(b) The district court entered a final judgment on February 21, 2014. A1. This Court has exclusive jurisdiction over this appeal under 28 U.S.C. § 1295(a)(1).

(c) Par timely filed a notice of appeal on March 18, 2014. A27869-70.

STATEMENT OF THE ISSUE

Whether the district court erred in holding that TWi proved by clear and convincing evidence that the asserted claims of the '576 patent are invalid as obvious.

INTRODUCTION

This case presents a challenge to the validity of a patent embodying path-breaking improvements to a drug (megestrol acetate) that all agree have provided enormous benefits to an especially vulnerable class of patients—HIV/AIDS patients suffering from anorexia and severe weight loss. The district court invalidated the asserted patent claims on the ground of obviousness.

At the time of the invention, megestrol acetate had been sold for more than 30 years in various dosage forms. An oral suspension dosage form ("Megace OS") had been sold for almost a decade to treat severe weight loss in anorexic HIV/AIDS patients. In 2002, the inventors of the '576 patent-in-suit discovered a previously unknown defect in Megace OS. Fasting patients—the very target patient population—barely absorbed the drug into their blood stream, whereas patients who took the drug after eating had 600-700% higher absorption. Not only was this food effect not known, but prior art taught **against** it—researchers routinely administered the drug to patients in a **fasted** state, believing that would result in optimal absorption. The '576 patent inventors not only discovered the food-effect problem, they invented a solution using what was, at the time, a relatively new and experimental technology—nanotechnology—that had previously been used in only one marketed drug product. Ultimately, the inventors developed an alternative product with a much smaller particle size that greatly

increased the fasted-state absorption and substantially eliminated the food effect. In HIV/AIDS patients, using the new formulation caused faster and greater weight gain. *See* A6077-86; A3215 (Tr. 38:6-39:4).

In its decision below, the district court agreed with Par that the patentees discovered and solved the previously unknown food-effect problem for Megace OS. Yet the court nevertheless found that the asserted claims were obvious. In doing so, the court not only disregarded the cardinal principle that "an invention can often be the recognition of a problem itself," *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1353 (Fed. Cir. 2013), but committed several errors of law that demonstrate precisely the sort of hindsight analysis this Court has condemned.

For example, since the food-effect problem the inventors solved was previously unknown, the district court instead pieced together claim limitations from a number of different references by inventing alternative motivations that are unconnected to the specific limitations in the claims at issue. This central legal error requires reversal, because the court "brush[ed] aside" the specific claimed invention and instead "collaps[ed] the obviousness analysis into a hindsight-guided combination of elements." *Id.* at 1354. The court summarily invoked the doctrine of inherency in an effort to solve that disconnect, but it failed to find that the specific limitations were inherent properties of anything, much less the inevitable result of combining the general teachings of the art upon which the court relied.

The court impermissibly discounted prior art that taught **away** from using a nanoparticulate megestrol acetate formulation. And the court improperly dismissed significant evidence of unexpected results and the solution to a long-felt and unmet need.

For any one of these reasons (or others discussed below), the judgment below should be reversed and the case remanded for further proceedings.

STATEMENT OF THE CASE

I. MEGESTROL ACETATE

The FDA originally approved megestrol acetate tablets to treat cancer in 1971. In 1993, Bristol Myers Squibb Company ("BMS") obtained FDA approval to market Megace OS, an oral suspension form of the drug. A2-3. This new formulation used micronized megestrol acetate, and was marketed to treat "anorexia, cachexia or [significant] unexplained weight loss" associated with HIV or AIDS. A3152 (43:8-44:17); *see* A5968-80.

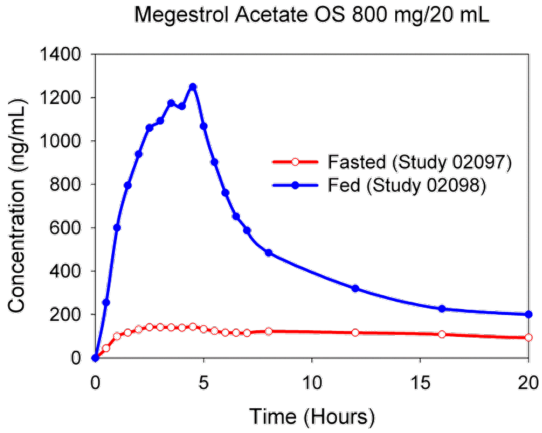
Megace OS was a commercial and medical success. A3. Several researchers reported that Megace OS increased body mass in AIDS patients suffering from severe weight loss. A3213 (31:25-32:10). By ameliorating wasting, the OS formulation decreased the associated risks of mortality, morbidity, hospitalization, an opportunistic infection. *Id.* And yet, despite this success, at this time skilled artisans did not appreciate that the drug had a serious absorption

problem in fasting patients, which prevented the drug from achieving its full potential in the target patient population. *See infra* at 5-9.

II. THE '576 PATENT AND THE ASSERTED CLAIMS

In 2002—nearly ten years after Megace OS entered the market—the '576 patent inventors began experiments with pharmaceutical formulations that dramatically reduced the particle size of megestrol acetate to the nanoparticulate range, to see if they could create an improved product. During their research, they made an entirely surprising and unexpected discovery: When patients took Megace OS (the micronized formulation) **without** food, they absorbed very little megestrol acetate into their blood streams. The maximum concentration of the drug in a patient's blood (the "C_{max}") was **600-700% lower** than for patients who took Megace OS **with** a high-fat meal. A7822-23; A8221 (Tables 2 & 3, Formulation D); A8228 (Tables 12 & 13, Ref. Treatment B); A3168 (23:17-24:17). In scientific terms, administering Megace OS in the "fasted state" resulted in low bioavailability, but administering it in the "fed state" resulted in much higher bioavailability. This difference in fed versus fasted bioavailability is called a food effect.

The food effect the patentees discovered for Megace OS was extreme:



A7824; *see* A7825; A3164-65 (5:8-10:7). This chart illustrates a 629% food effect[1] for Megace OS found in one of Par's studies.

This dramatic food effect was a significant problem because it prevented the intended patient population—**anorexic** patients who often took the drug on an empty stomach—from receiving the full benefit of the drug.

The inventors' discovery of the food effect defied conventional wisdom. A3164-65 (5:3-7, 11:2-8); A3167 (20:19-24); A3161 (77:23-78:1). It was contrary to the widespread and consistent administration of Megace OS to patients in the fasted state, A3161 (78:2-79:2), and the practice of experienced clinicians who treated HIV patients for weight loss and wasting, A3211 (21:5-9). At the

[1] Here, the percent difference in "fed versus fasted" absorption is the percentage amount the fed C_{max} exceeds the fasted C_{max}. *See* A7822-23. The formula is (Fed C_{max} - Fasted C_{max})/Fasted C_{max}. *See* A3185 (90:3-7). For example, the 629% difference above = (1364 - 187)/187.

time of the discovery, no one had reported the fasted-state Megace OS bioavailability problem.

Not only did the inventors discover the problem, they also developed a solution. Using a then-experimental approach for formulating pharmaceuticals (nanotechnology), they developed a nanoparticulate formulation that drastically reduced the food effect from a range of 629-787% to a range of 8-55%, as shown in the table below.

Formulation	Study	Dose	Condition	C_{max} (ng/mL)	% Diff.
Nanoparticulate (Megace ES)	02097	150 mg	Fasting	412	8%
	02098		Fed	379	
	02097	250 mg	Fasting	647	9%
	02098		Fed	588	
	30146	375 mg	Fasting	810	18%
	30147		Fed	958	
	02097	450 mg	Fasting	955	13%
	02098		Fed	1,079	
	30422	675 mg	Fasting	1,044	55%
	30422		Fed	1,616	
Original (Megace OS)	02097	800 mg	Fasting	187	629%
	02098		Fed	1,364	
	30146	800 mg	Fasting	193	787%
	30147		Fed	1,711	

See A7822-23; A3168-69 (24:19-26:10); A8228 (Tables 12 & 13, Treatments A, C, D). Par's expert Dr. Fleckenstein explained that this discovery represented a "substantial reduction in food effect" that was "among the largest" he had seen in his career. A3169 (28:7-14).

The elimination of the food effect represented a significant breakthrough for anorexic/wasting patients, whose condition means they are frequently not eating. A3213-16 (30:24-42:9). As a result of the discovery, the FDA-approved label—in stark contrast to Megace OS—states that the '576 commercial embodiment Megace ES[2] can be taken "without regard to meals." A4; A5956-67 at 5957; A27628-29 ¶4. In a clinical trial comparing the efficacy of 575 mg of a claimed nanoparticulate formulation with the recommended 800 mg dose of Megace OS, A6077-87 at 6077, patients given the claimed formulation gained substantially more weight (1.5 times more after 12 weeks) than patients given Megace OS.

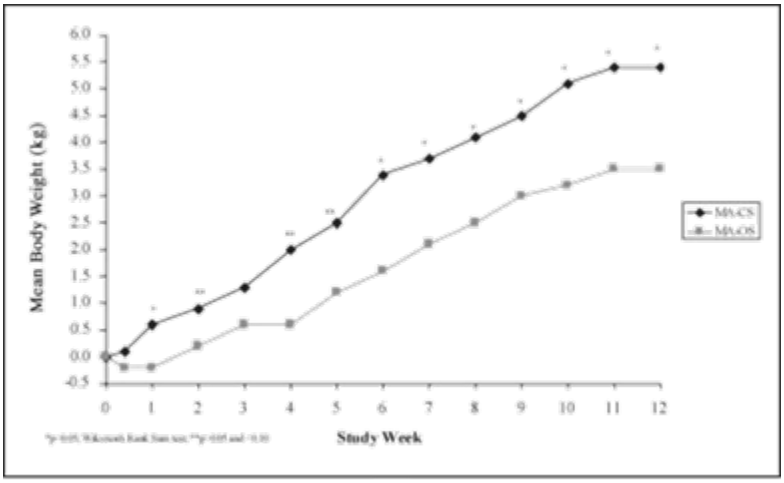


Figure 1. Mean body weight change from baseline.
*P<0.05, Wilcoxon's Rank Sum Test; **P>0.05 and <0.10
MA-CS = megestrol acetate concentrated solution; MA-OS = megestrol acetate oral suspension

A6080; A3214 (33:11-17); A3215 (38:6-39:4). The claimed formulation also led "to greater weight gain in a shorter period of time." A3214 (34:2-9). The results

[2] Par licensed the Megace name from BMS.

at the beginning of treatment are important. As seen above, patients taking Megace OS continued to **lose weight** during the first week of therapy, while patients taking the inventive formulation (at a 28% lower dose) gained more than 0.5 kg in that first week. A6080; A3215 (38:20-25); *see also* A3216 (41:14-42:9) (the weight gain shown in the study was "quite clinically meaningful"). This result suggests that while Megace OS eventually caused some weight gain because the patients slowly built up megestrol acetate as they continued to take the drug over time, its poor fasted-state absorption both delayed and reduced its effect. The claimed invention, on the other hand, absorbed effectively in the fasted patients and started to work much sooner.

Megace ES has generated more than $600 million in net sales since its launch in 2005. *See* A3244-45 (52:17-55:17).

The asserted '576 patent claims are narrowly tailored to this advance in fasted-state bioavailability and the corresponding reduction in food effect. Claim 1 covers:

> 1. A method of increasing the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass, comprising administering to the human patient a megestrol formulation, wherein:
>
> (a) the megestrol acetate formulation is a dose of about 40 mg to about 800 mg in about a 5 mL dose of an oral suspension;
>
> (b) the megestrol acetate formulation comprises megestrol particles having an effective average particle size of less than about 2000 nm,

> and at least one surface stabilizer associated with the surface of the megestrol particles; and
>
> (c) the administration is once daily;
>
> wherein after a single administration in a human subject of the formulation there is **no substantial difference in the C_{max} of megestrol when the formulation is administered to the subject in a fed versus a fasted state**,
>
> wherein fasted state is defined as the subject having no food within at least the previous 10 hours, and wherein fed state is defined as the subject having a high-calorie meal within approximately 30 minutes of dosing.

A8228 (41:64-43:8).[3]

Other asserted claims have limitations requiring different pharmacokinetic parameters. The other asserted independent claim—claim 4—has largely the same limitations as claim 1, except that the fed-fasted difference in C_{max} is selected from a defined list of percentages starting at 100%. A8229 (3:15-41). The asserted dependent claims add several limitations, including claim 5 (difference in C_{max} is less than about 60%); claims 12, 13, 26, and 27 (maximum blood plasma concentration of at least about 700 ng/ml in the fasted state); claims 14 and 28 (maximum blood plasma concentration of at least about 400 ng/ml in the fasted state); claims 15 and 28 (a mean C_{max} of about 300 to about 2000 ng/ml is obtained after single fasted-state administration). A8229-30 (43:42-46:45). All these

[3] Emphasis added unless otherwise stated.

limitations relate to the reduced food effect, which provides actual clinical benefit. A3169-70 (28:7-29:4).

In addition to the pharmacokinetic parameters, claims 2, 10, 21, and 24 limit the administration of the drug to HIV/AIDS patients. A8229-30 (43:9-46:21).

III. PRIOR-ART KNOWLEDGE REGARDING MEGESTROL ACETATE

A. The Prior Art Taught That Rapid Absorption Resulted In Poor Weight Gain

Graham was a seminal study on the "pharmacokinetics and pharmacodynamics of megestrol acetate in patients with human immunodeficiency virus (HIV) infection." A15924-34 at 15928. Graham is a "particularly important" reference identified in the Megace OS monograph. A3095 (45:15-24); A3155 (55:24-56:1). First, Graham taught that the efficacy of megestrol acetate **was not correlated** to the total amount of drug absorbed into the bloodstream (called "AUC"). A3173 (42:13-44:7).

Second, Graham taught that "more rapid absorption" was **undesirable** and would lead to a **poorer** clinical response. *Id.* (43:10-44:7). In the study, patients were classified into two groups based on their absorption of the drug. *See* A15932; A3173 (43:16-18). The first group of patients (the "1-compartment" model) had a "slower" and "more sustained" absorption of megestrol acetate, and exhibited superior weight gain (3.6 kg, or about 7.9 pounds). *See* A15932; A3173-74 (43:19-44:1, 44:25-45:4). The second group of patients (the "2-compartment"

model) had "more rapid absorption" of the drug, but **gained no weight**. *See* A15932-33; A3173 (43:22-24, 44:20-24).

Graham taught skilled artisans that merely increasing megestrol blood levels would not increase weight gain, and that more rapid absorption of the drug would result in poorer patient outcomes.

Graham also noted a high degree of interpatient variability in megestrol pharmacokinetics, and in response to therapy. A15930, 15932. But neither Graham nor any other prior art attributed this interpatient variability to an issue of bioavailability, to a food effect, **or to any issue that could be addressed by changing the formulation**. To the contrary, Graham specifically concluded that the variability was caused by **other factors specific to the HIV/AIDS patients** being studied, such as enteropathy (loss of gut function), achlorhydria (low stomach acid), and concurrent HIV/AIDS medications. A15932-33; A3172-73 (40:8-41:20). Serious weight loss accompanying HIV/AIDS does not have a single etiology or root cause, but is a symptom engendered by a wide variety of different causes. A3213 (30:24-31:24). Accordingly, the varied responses of these seriously ill patients to megestrol acetate therapy did not suggest any deficiency in the existing Megace OS formulation; the issues were unavoidable ones endemic to the disease.

B. The Substantial Food Effect For Megestrol Acetate Was Unknown In The Prior Art

Before the '576 patent, it was not known that megestrol acetate oral suspension exhibited poor fasted-state bioavailability. A3163-64 (4:25-5:7).

Megace OS *label and monograph*. The FDA-approved prescribing information for Megace OS, A5968-80, does not instruct the patient to take the medication with (or without) food. A3161 (77:5-78:1). To the contrary both the label and the monograph state: "The effect of food on the bioavailability of MEGACE Oral Suspension has not been evaluated." A5970; A14927-36 at 14930. TWi's expert characterized the monograph as "the one source of comprehensive valid information about the active pharmaceutical ingredient." A3094 (42:19-25, 43:8-20).

***Graham, Oster, Camaggi, and Farinha*.** Scientific articles by Graham (1994), Oster (1994), Camaggi (1995), and Farinha (2000) discussed the use of megestrol acetate. In each case, the investigators administered megestrol acetate in the fasted state. A3161 (78:2-79:2); A15929; A6064; A6044-47 at 6045; A6050-54 at A051. This pattern shows that prior-art researchers "believed that the drug was optimally absorbed in the fasting state"—because these studies involved severely ill AIDS and advanced cancer patients, A15924-34; A6062-71; A6044-47, where the investigators were highly motivated and ethically compelled to administer the drug under optimal conditions. A3161 (79:3-25); A17, 19.

Other Prior Art. Dr. Fleckenstein conducted an extensive literature search and found no evidence of any food effect or of any recommendation that Megace OS be taken with food published prior to the invention. A3160 (74:19-21, 76:8-12). Dr. Wanke, who personally prescribed Megace OS to treat wasting in HIV/AIDS patients, confirmed clinicians at the time "did not know that we should be telling patients who were prescribed Megace [OS] that they should be taking it with food." A3210-11 (20:9-23:4); A19.

FDA Guidance. A 2002 FDA guidance addressing food effects for drug products generally, underscored the unpredictability of the food effect for drug formulations of poorly water-soluble drugs, which include megestrol acetate:

> [F]ood effects are most likely to result from a more complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance. In these cases, **the relative direction and magnitude of food effects** on formulation BA [bioavailability] and the effects on the demonstration of BE [bioequivalence] **are difficult, if not impossible, to predict** without conducting a fed BE study.

A6024-35 at 6028.

C. Prior Art Regarding Megestrol Acetate Formulations

Several groups of skilled artisans formulated and reformulated megestrol acetate oral suspensions between when Megace OS entered the market and the time of the invention. *See* A6019-23(Atzinger); A6088-92 (Ragunathan); A16604-11 (Brubaker). Notably, these artisans were working directly with megestrol

acetate oral suspensions, but none suggested any bioavailability or food-effect problem with any of the suspensions studied. And even though the key nanoparticulate references (Liversidge/Elan) were available during this time, none of the scientists working on megestrol acetate even suggested altering particle size, much less using a nanoparticulate approach. A3157 (62:12-63:11). Indeed, all three references recommended the identical micronized size range (3 to 10 microns) as "preferred." *See* A6020 (2:51-54); A6090 (4:64-67); A16607 (¶ 0033). For example, Brubaker (2002) explored various modifications to make "pharmaceutically elegant," A3157 (63:1-5), enhancements to the existing megestrol acetate oral suspension formulation. A3183 (82:1-84:12). To do this, Brubaker "altered a variety of things," including surfactants, suspending agents, pH buffers, and protective colloids, "but did not alter the particle size." A3181 (74:13-75:1); *see* A16607-08 (¶¶ 0034-47).

IV. PRIOR ART REGARDING NANOPARTICULATE TECHNOLOGY

As of 2002, nanoparticulate technology was an experimental and unproven approach for formulating pharmaceuticals. At that time only a single marketed pharmaceutical product—a tablet of the immunosuppressant drug Rapimmune®—used nanoparticulate technology. No marketed oral suspension formulations used nanoparticulate technology.

Nanoparticulate technology was a very general approach to formulating drugs, and involved multiple steps, ingredients, and variables. References suggested it could be used to make tablets, capsules, powders, injectable and inhaled dosage forms, and a host of other potential formulations. *See* A14953-63. In general, as the particle size of a pharmaceutical solid is reduced, the smaller particle size causes an increase in total surface area for the same amount of drug. But as the particle size continues to decrease, there is an increase in the attraction between the particles, causing a tendency for them to agglomerate or "clump" into larger particles. To avoid this problem, the small particles must be stabilized using surface stabilizer(s). In a liquid suspension formulation, the solvent, the surface stabilizers and other ingredients must be selected so that the small particles do not clump into larger particles during the product's shelf life.

The prior art regarding nanoparticulate technology—much of it published by plaintiff Alkermes and its predecessor-in-interest Elan—primarily addressed this first step to creating nanoparticulate drug formulations, specifically creating the nanoparticles themselves.

Liversidge '684 patent (1992). The '684 patent, A14887-97, concerns the manufacture of nanoparticles. A3176 (56:12-16). It specifies that the nanoparticles are stable for **15 minutes or preferably two days**. A14892 (7:43-46); A3069 (74:14-21). While such nanoparticles were a significant advance for

investigational purposes, many significant steps remained to develop a marketed pharmaceutical product. A3069 (74:22-75:22); A14961. The '684 patent does not disclose using nanotechnology with megestrol acetate. A3068-69 (72:22-73:1); *see also* A8208 (1:20-21).

Liversidge '363 patent (1995) and EP '215 patent (1994). The '363 patent, A14876-86, is a continuation of the '684 patent. A3052 (7:20-22). The '363 patent discloses that nanoparticulate technology can be used to make injectable dosage forms of anticancer agents that could not previously be administered intravenously. A14881 (8:11-16); A3069 (75:23-76:18); A3128 (76:18-21); A3175 (50:13-51:5). Again, the '363 patent describes nanoparticles that are **stable for 15 minutes, or preferably two days or longer**. A14881 (7:40-42). The '363 patent includes megestrol acetate in a list of thousands of potential candidate anticancer compounds and categories of compounds, but does not describe any actual formulation of the drug. A14878-79 (2:50-3:49); A3175 (51:6-25). All of the example dosage forms disclosed were injectable. A3128 (76:18-21).

The EP '215 patent, A14937-52, is essentially the European counterpart to the '363 patent with essentially identical disclosures. A3175-76 (50:13-51:5, 55:11-16).

***Elan brochure*.** The Elan brochure, A14953-63, contains marketing material advertising Elan's NanoCrystal technology. A3177 (59:9-13). The brochure highlights the experimental state of the technology, suggesting that "Elan can effectively partner with pharmaceutical companies in the development phase to increase the generation of lead compounds." A14953; *see* A3177-78 (59:17-62:2). The Elan brochure states that only "[o]ne product incorporating NanoCrystal® technology has been approved by regulatory authorities for marketing in the United States," and highlights that it "is currently being applied to over 30 **development** compounds." A14953. The Elan brochure does not mention megestrol acetate. A3177 (59:14-16).

***Müller*.** Müller summarized purported benefits of Elan's NanoCrystal technology, repeating the same list of potential advantages discussed in the Elan Brochure. A14972-98; A3115 (21:18-22:2, 22:15-23:3). Müller explained that the impact of nanoparticulate formulation was yet to be determined. A3177 (58:4-18).

V. THE PATENT PROSECUTION HISTORY

The inventors filed for patent protection on their new nanoparticulate-based method in 2002. A8196-231. The patent examiner expressed the same understanding as the megestrol acetate prior art: "[o]ne of ordinary skill in the art would be further motivated to use the fasted state" for megestrol acetate. A6613-19 at 6617.

The examiner granted the '576 patent in 2006, after requesting that the inventors add the fed/fasted limitations to the claims. *See* A14785, 14726-34, 14711-22, 14797, 14802-07. Specifically, the patentee added the fed/fasted "wherein clauses" to the claims—*e.g.*, "wherein after a single administration ... there is no substantial difference in the C_{max} of megestrol" between the fed and fasted states (claim 1); "the difference in the C_{max} of megestrol" between the fed and fasted states is less than 100% (claim 4); "difference in C_{max} is less than about 60%" (claim 5). A14726-27.

The examiner found the amended claims patentable over the prior art, including Brubaker and the principal nanotechnology references (the '684, '363, and EP '215 patents). *See* A3180 (72:18-20); A3175-76 (50:9-12, 55:8-10); A8198 (col. 1) (references cited).

VI. THE DISTRICT COURT PROCEEDINGS

TWi submitted an Abbreviated New Drug Application for a generic version of Megace ES, containing a "Paragraph IV certification," pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the '576 patent "is invalid or will not be infringed" by TWi's generic drug. A20003 ¶15. In response, Par filed this infringement action against TWi. A20001-50.

TWi moved for summary judgment of noninfringement and invalidity, and Par cross-moved for partial summary judgment on two of TWi's invalidity

defenses. The district court granted Par's summary judgment motion and substantively denied TWi's motion as relevant here. A25133-58. Rejecting TWi's noninfringement argument, the court construed the "wherein" clauses as substantive claim limitations "[b]ecause the beneficial lack of a food effect is **the central defining characteristic** of the method of treatment claimed in the '576 patent." A25143.

In granting Par summary judgment on TWi's anticipation defense, the court found that the '363 patent—regarding nanoparticulate formulations of injectable anticancer compounds—"permits a nearly limitless array of drug formulations and delivery mechanism combinations, which cannot plausibly be held to have 'necessarily' enabled the development and implementation of the specific method claimed in the '576 patent targeting the treatment of wasting diseases using a drug without a substantial food effect." A25153. The parties then stipulated that, under the district court's construction, TWi's product would infringe the '576 patent. A27623-25.

The district court held a five-day bench trial to resolve TWi's remaining defenses of patent invalidity and its challenge to Par's standing as co-plaintiff. A2. TWi's lead argument at trial was that, at the time of the invention, the prior art disclosed "a need for improved bioavailability." A3008 (30:19-24). TWi's witnesses did not provide any opinions that any claim limitations were inherent.

Following trial, the court concluded that the patent was invalid as obvious. A42. The district court rejected TWi's lead argument that it was known at the time of the invention that Megace OS had a bioavailability problem and related food-effect problem. A10-20. Specifically, the court found that TWi's evidence did not demonstrate "a known bioavailability problem with Megace OS"—the micronized suspension formulation. A13. TWi's evidence demonstrated that "megestrol acetate itself [*i.e.*, non-micronized] was not fully bioavailable," but the evidence did not demonstrate that one "would have known that micronizing the particles did not fully resolve the bioavailability issues." *Id.*

The court concluded that TWi's evidence "does not convincingly demonstrate that, by April 2002, one skilled in the art would have known the extent of Megace OS's bioavailability, or that Megace OS, or megestrol acetate for that matter, was more effectively absorbed when taken with food." A15. The fact that the food effect was unknown was "further bolstered by the fact that Graham and other researchers, in several studies conducted in 1994, 1995, and 2000, instructed participants to take Megace OS without food." A19.

The court then addressed the prior art regarding nanotechnology—relying on seven different references. The court emphasized that the prior art taught that increased bioavailability was the key benefit of nanoparticulate formulations of

drugs—even though TWi had not demonstrated a known bioavailability problem with Megace OS. A20-24.

After discussing approximately 20 prior-art references, the court found that the prior art disclosed "every element" of the claims, and found a "prima facie case of obviousness." A24. Without explaining on a claim-by-claim basis where the specific pharmacokinetic parameters in the claims were disclosed in the prior art, the court generally stated that the "pharmacokinetic parameters with respect to a food effect … are inherent properties of the obvious nanoparticulate formulation claimed by the '576 patent." A25-26.

The court then analyzed whether there was a motivation to combine the prior art references. The court explicitly rejected TWi's lead motivations—food effect and bioavailability—but instead found "other motivations." A28. Specifically, the court relied on two purported problems as providing sufficient motivation "to create a method of treatment using nanoparticles": (1) Megace OS was "viscous and required more dosing," and (2) "absorption levels varied greatly among patients." A29. According to the court, a reduction in particle size was a known solution for all of these problems. A33.

The district court rejected Par's argument that the Graham reference taught away from the claimed invention. A33-34.

Finally, the court rejected Par's arguments that secondary considerations undermined any assertion of obviousness. A35-41. Among other things, Par had presented extensive evidence that the claimed invention produced unexpected results—the inventors discovered and solved the food effect and fasted-state bioavailability problems. The district court dismissed the evidence of unexpected results on the ground that it was unrelated to the motivations to combine—viscosity and interpatient variability—that the court had previously identified. A37 ("The fact that the use of nanotechnology may have surprisingly solved other problems as well does not undermine that finding.").

Plaintiffs appealed.

SUMMARY OF ARGUMENT

The district court's judgment of invalidity should be reversed because TWi failed to prove by clear and convincing evidence that the '576 patent is obvious. The inventors made a startling and important discovery: Megace OS, which had been used for years to treat anorexic patients, was barely absorbed when taken without food. In other words, the very ailment that the drug was intended to help was preventing it from working as effectively as it could. This food effect was completely unknown before the invention, prior art taught **away** from giving patients the drug in a fed state, and patients were consistently given the drug without food.

The inventors solved this significant problem using a then-experimental and unproven approach (nanotechnology) and inventing a method using a nanoparticulate formulation of megestrol acetate that reduced the food effect from a range of 629-787% to a range of 8-55%. *See* A7822-23; A3168-69 (24:19-26:10). The change was drastic, and translated into significant, tangible benefits for patients. They gained weight in a shorter period of time and gained more weight. *See* A3214 (33:11-17, 34:2-9). After 12 weeks, patients taking a lower dose of the claimed formulation gained 1 ½ times greater weight than the patients taking Megace OS. A6077-78; A3215 (39:1-4).

The district court agreed with Par that the food effect was unknown prior to the invention and was an important discovery for the treatment of AIDS. A10-20. That alone is strong evidence of nonobviousness. Indeed, it is well-established that "an invention can often be the recognition of a problem itself." *Leo*, 726 F.3d at 1353. Yet, the court nevertheless reached the counter-intuitive conclusion that the claims at issue were invalid as obvious. In doing so, the court committed several independent errors that ultimately are products of a forbidden hindsight analysis and require reversal.

First, the district court reasoned that problems of viscosity and interpatient variability would have motivated a skilled artisan to create the claimed invention. But it is well settled that the patent challenger must show that "there was an

apparent reason to combine the known elements **in the fashion claimed by the patent at issue**." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The district court failed to connect its asserted motivations of viscosity and interpatient variability to the claims at issue—which were specifically directed to solving the food effect (and not viscosity or interpatient variability). And, indeed, there is no evidence that one motivated to solve viscosity and interpatient variability problems would have created the specific claimed method, which addressed the food effect in specific ways defined by the patent's claim limitations.

Second, the court tried to avoid the legal error in its motivation analysis by treating the food-effect limitations as inherent characteristics of the invention that were irrelevant to the obviousness analysis. But that was error because TWi failed to meet the standard for proving inherency—that the missing limitation is "necessarily present" in the prior art. *See, e.g.*, *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). TWi provided no evidence—much less clear and convincing evidence—that the specific food-effect limitations invariably and necessarily result from all nanoparticulate formulations of megestrol acetate.

Third, aside from these legal errors, the district court's analysis is flawed because its asserted motivations—viscosity and interpatient variability—would not have motivated one to use nanotechnology **at all**. The prior art never identified viscosity or interpatient variability as problems with the existing Megace OS

formulation. And even if they were known problems, the prior art did not teach that nanotechnology would have solved the problems. Moreover, nanotechnology was a new, experimental process, and artisans would have looked to manifold other, more established solutions to improve the drug.

Fourth, the district court erroneously rejected Par's unrebutted showing that the prior art taught away from the claimed invention. Nanotechnology was promoted to cause rapid absorption, but the leading study of Megace OS in HIV/AIDS patients—Graham—taught that rapid absorption resulted in no weight gain.

Finally, the district court erroneously discounted the objective indicia of nonobviousness. There was overwhelming evidence that the invention surprisingly and unexpectedly solved the food effect, which was "very dramatic" and "among the largest food effect[s]" that Dr. Fleckenstein had seen. A3165 (11:2-8); A3169 (28:11-14). The district court committed a legal error by disregarding this evidence solely on the ground that it was unrelated to the motivations the court had identified (viscosity and interpatient variability). Moreover, there was unrebutted testimony that Megace ES solved a long-felt and unmet need, resulting in "a greater degree of weight gain" in HIV/AIDS patients compared to Megace OS, and that the difference was "quite clinically meaningful." A3216 (41:16-23).

For these reasons, the district court erred in invalidating the important patent at issue in this case on the ground of obviousness. Its judgment should be reversed and the case remanded for further proceedings.

STANDARD OF REVIEW

Obviousness is a question of law, which this Court reviews de novo. *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1365 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 1736 (2013). The obviousness conclusion is based on underlying factual determinations, which are reviewed for clear error. *Id.* The factual inquiries are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the art; and (4) objective considerations. *Id.* at 1365-66. "While [this Court] afford[s] deference to a district court's factual findings, however, [it] retain[s] plenary review to determine whether, as a legal matter, the evidence satisfies the clear-and-convincing standard of proof." *In re Cyclobenzaprine*, 676 F.3d 1063, 1069 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 933 (2013).

ARGUMENT

THE DISTRICT COURT ERRONEOUSLY HELD THE ASSERTED CLAIMS INVALID AS OBVIOUS

Patents are presumed valid. 35 U.S.C. § 282. Invalidity for obviousness, 35 U.S.C. § 103, must be established by clear and convincing evidence. *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012).

This is a high burden, requiring "evidence that produces an abiding conviction that the truth of [the] factual contentions are highly probable." *Id.* at 1327 (alteration in original) (citation and internal quotation marks).

The challenger to a patent's validity retains a clear-and-convincing burden of proof on all issues, and that burden never shifts during litigation. *Cyclobenzaprine*, 676 F.3d at 1079-80. Here, the district court determined that TWi had established a prima facie case of obviousness, A24, and that the objective evidence of nonobviousness did not undermine that determination, A37. Both determinations, and the court's obviousness conclusion, were error.

A. The District Court Erroneously Found A Prima Facie Case Of Obviousness

The district court erred in concluding that TWi established a prima facie case of obviousness. A patent "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Indeed, "most, if not all" inventions "rely upon building blocks long since uncovered," so it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* Accordingly, the challenger of the patent must "show by clear and convincing evidence that a skilled artisan would have been **motivated to combine** the teachings of the prior art references to achieve the claimed invention, and ... would have had a **reasonable expectation of success** in

doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007); *see also Cyclobenzaprine*, 676 F.3d at 1068-69.

Identification of a motivation to combine the prior art elements is "the best defense against hindsight-based obviousness analysis." *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000). It is particularly important when—as here—elements from multiple different references are involved. A party cannot simply "pick and choose among individual parts of assorted prior art references as a mosaic to recreate a facsimile of the claimed invention." *Akzo N.V. v. ITC*, 808 F.2d 1471, 1481 (Fed. Cir. 1986) (citation and internal quotation marks omitted); *accord Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352-53 (Fed. Cir. 2013), *cert. denied*, 134 S. Ct. 1542 (2014). Indeed, the Supreme Court "recognized in *Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809 (1986), that ... 'a judge must not pick and choose isolated elements from the prior art and combine them so as to yield the invention in question if such a **combination** would not have been obvious at the time of the invention.'" *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008) (citation omitted).

The district court here engaged in precisely the type of prohibited hindsight reconstruction this Court has warned against, committing multiple errors.

1. The District Court's Motivations Do Not Lead To The Specific Claims At Issue

The district court purported to find the individual elements of the claimed invention from an assortment of prior-art references, and then it invented motivations to combine those elements. There is a fundamental disconnect between the motivations upon which the district court relied and the claimed invention.

The district court found that the problems of viscosity and interpatient variability would have motivated a skilled artisan to produce **a** nanoparticulate formulation of megestrol acetate. A29. The court repeatedly stated its conclusion in those general terms: the problems provided a motivation "to create a method of treatment using nanoparticles," *id.*, "to use nanoparticles to reformulate the drug," A30, "to apply[] the nanoparticulate technology disclosed in the prior art," A28, and to "combin[e] nanotechnology with megestrol acetate," A26. But motivation to create **a** nanoparticulate **formulation** of megestrol acetate is not the same thing as motivation to create **the specific claimed method**. That is like saying that because there was a motivation to knit a sweater, there was a motivation to use a double basket weave stitch to knit a half-inch thick sweater with specified heat-retention properties.

The court never explained—and TWi presented no evidence of—how viscosity and interpatient variability would supposedly lead one to create the

specific, claimed method to achieve particular claimed results directly related to the food effect. The specific claim limitations in the patent define the scope of the claimed invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). Here, the limitations in the asserted claims are based on pharmacokinetic properties associated with eliminating the food effect:

Claim(s)	Requirement
1	after a single administration of the drug "there is **no substantial difference** in the C_{max} of megestrol" between the fed and fasted states
4	after a single administration of the drug "the difference in the C_{max} of megestrol" between the fed and fasted states is **less than 100%**, …
5	Fed/Fasted difference in C_{max} is "**less than 60%.**"
12, 26	Maximum blood plasma concentration[4] of **at least about 700 ng/ml**
14, 28	Maximum blood plasma concentration of **at least about 400 ng/ml**
15, 29	C_{max} about **300 to about 2000 ng/ml after single fasted administration**

There was no evidence that a person of ordinary skill in the art who was trying to address viscosity and interpatient variability problems would have

[4] "[M]aximum blood plasma concentration" is defined in the '576 patent to mean under fasting conditions. A8220 (25:7-9).

combined the art the way the court did to create a nanoparticulate formulation with these claimed parameters. The court never connected the motivations it identified with the specific limitations in the claims at issue—indeed, it never even mentioned them.

That was a legal error. A patent challenger must show "there was an apparent reason to combine the known elements **in the fashion claimed by the patent at issue**." *KSR*, 550 U.S. at 418. This Court has likewise rejected obviousness claims based on general testimony about a motivation to combine that fails "to explain why a person of ordinary skill in the art would have combined elements from specific references **in the way the claimed invention does**." *ActiveVideo Networks*, 694 F.3d at 1328 (emphasis in original). To prevent hindsight bias, there must be evidence "as to how or why the references would be combined to **produce the claimed invention**." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008).

Specific claim limitations cannot be ignored in the obviousness analysis. In *Cyclobenzaprine*, this Court held that the district court erred by failing to consider claim limitations "requiring therapeutic effectiveness, and whether it would have been obvious to one of ordinary skill in the art at the time of the invention that [the asserted obvious formulation] would satisfy that limitation." 676 F.3d at 1069. Likewise, in *Abbott Laboratories v. Sandoz*, the defendant argued that the patented

extended release formulation of the drug was obvious because the "principle of using controlled release formulations to reduce the dosing frequency for short half-life compounds" was known and "no more than routine experimentation was needed to find a controlled release formulation that would meet the pharmacokinetic requirements stated in the [patent] claims." 544 F.3d at 1347. The district court rejected the argument, and this court affirmed, because one of ordinary skill in the art "would not have predicted **which formulation**, that might be selected from the prior art, would provide the **required pharmacokinetics**." *Id.* at 1349, 1352-53. So too here. The district court erred by failing to connect the motivations it identified—viscosity and interpatient variability—to the food-effect limitations in the patent.

Obviousness can be found based on motivations other than those identified by the patentee, *KSR*, 550 U.S. at 419, but only when the alternative motivation would lead the skilled artisan to combine all of the claim elements, as claimed. *KSR* involved a straightforward combination of three mechanical features: a particular gas pedal with a particular sensor, in a particular location. The Court sanctioned the consideration of any prior-art motivation that would lead a person to combine those elements in the claimed fashion. *Id.* The reason for combining those elements would not have altered the way in which they were combined.

But consistent with *KSR*, this Court has rejected "alternative" motivations that do not yield the claim limitations that spring from the inventor's motivation. In *Alcon Research v. Apotex*, the Court relied on a different motivation than the inventor's to find independent claims obvious, 687 F.3d at 1369, but found certain dependent claims nonobvious because they specified a dosage range that would have been useful only for the inventor's purpose, *id.* at 1370-71. Similarly, in *Allergan, Inc. v. Sandoz Inc.*, the court found obvious one patent involving a certain drug combination, but found a similar patent nonobvious because it contained the additional limitation "that the daily number of doses ... be reduced from 3 to 2 times a day **without loss of efficacy**." 726 F.3d 1286, 1293 (Fed. Cir. 2013). As with the dependent claims in *Alcon* and the narrower patent in *Allergan*, the district court's motivations—viscosity and interpatient variability—would not have led to the specific claim limitations at issue, which pertain to the obviation of the food effect that the patentees discovered.

Further, to the extent the court relied on Megace OS "steady-state C_{max} levels"—reported after 21-day administration of Megace OS where patients were permitted to eat—as disclosing the fasted, single-dose C_{max} claim elements (see A25) that would constitute clear error. Disclosing a steady-state C_{max}—which includes residual amounts of the drug that build up over time—does not disclose, suggest or enable a similar fasting, single-dose C_{max}. A3121-22 (47:19-49:7). For

a fasted, single-dose C_{max} as claimed, the prior art Megace OS formulation was unable to even reach 200 ng/mL, which is far outside of the claimed ranges. A3164 (6:17-7:6); A7822-25.

2. The District Court Improperly Relied On Inherency To Disregard The Food-Effect Limitations

The district court tried to gloss over the disconnect in its motivation analysis by summarily declaring the food effect limitations inherent—and thus irrelevant. Addressing only claims 1, 4, and 5, the court stated that the "claimed pharmacokinetic parameters with respect to a food effect ... are inherent properties of the obvious nanoparticulate formulation claimed by the '576 patent." A26. But inherency does not work to fill in the missing link between the court's motivations and the specific claim limitations at issue. At the outset, the court did not even address the specific pharmacokinetic parameters in any of the dependent claims (except for mentioning claim 5 in passing), so it cannot bridge the gap for those claims.

More fundamentally, the district court did not find—and TWi did not put forward any evidence—that the **specific limitations** were inherent properties of anything, much less the inevitable result of combining the general teachings of the nanotechnology art with the art concerning megestrol acetate/Megace OS. For example, the district court did not find that a nanoparticulate formulation—created to solve viscosity and interpatient variability problems—would necessarily result

in "no substantial difference" in the C_{max} of megestrol between the fed and fasted states (claim 1), reduce it below 100% (claim 4) or 60% (claim 5), or result in a fasted-state, single-dose C_{max} of >700 ng/ml, >400 ng/ml or >300 ng/ml. *See* A8228-29 (42:55-44:28).

This Court has set a high standard for inherency. Limitations are inherent properties only when the property is "necessarily present." *See, e.g., In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) ("the Kubin-Goodwin application itself instructs that CD48 binding is not an additional requirement imposed by the claims on the NAIL protein, but rather a property **necessarily** present in NAIL"); *Alcon*, 687 F.3d at 1369 (the "stabilizing conjunctival mast cells" limitation "does not impose any additional requirement because the '805 patent itself **defines** mast cell stabilization as a property that is **necessarily** present at those concentrations"); *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) ("To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is **necessarily** present in the thing described in the [prior art] ...." (citation and internal quotation marks omitted)). Inherency cannot "be established by probabilities or possibilities." *Talbert Fuel Sys. Patents Co. v. Unocal Corp.*, 275 F.3d 1371, 1378 (Fed. Cir. 2002) (citation and internal quotation marks omitted), *vacated on other grounds*, 537 U.S. 802 (2002). "The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* (citation and

quotation marks omitted); *see also In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993).

That high standard was not met. The district court did not even purport to find that the **specific limitations** in the claims at issue were "necessarily present" whenever the general approach of nanotechnology would be combined with megestrol acetate for the purpose of addressing viscosity or interpatient variability issues. Instead of finding that a nanoparticulate formulation would have "no substantial difference" between the fed and fasted states (claim 1), or achieve the specific percentage differences outlined in claims 4 and 5, the district court merely found that a nanoparticulate formulation would **reduce** the food effect. The court stated: "As Dr. Beach testified, an improvement in bioavailability necessarily results in a **reduction** in any food effect, whether previously known or not."[5] A27. And it continued—without citation—that "TWi has demonstrated that reducing particle size will improve bioavailability across all administrations claimed in the invention, thus any food effect will inherently be **reduced**." *Id.*

[5] Dr. Beach's testimony at trial was limited to the a reduction in food effect. *See* A3112 (11:11-13) ("Improvement in bioavailability will necessarily affect the other two, meaning **reduce** interpatient variability and **reduce** food effect."); *id.* at 11:25-12:2 ("[T]he food effect is **diminished** because the drug will dissolve in GI fluids, whether it is a fasted state or whether it is a food state.").

By its own terms, the court's broad conclusion that smaller particles would "reduce" the food effect does not establish that the specific limitations in claims 1, 4 and 5, and the other dependent claims are inherent properties. The alleged general relationship between particle size and bioavailability does not say anything about what particle size is necessary to achieve specific pharmacokinetic properties. And it completely fails to account for the many other factors that go into formulating the drug, including, without limitation, the dose concentration and the surface stabilizer claimed in the patent.

Both parties' experts testified that nanoparticulate formulations of a drug could exhibit different pharmacokinetic properties due to numerous variables that could be adjusted. Dr. Beach—TWi's expert—agreed that nanoparticulate formulations of drugs can have many different characteristics depending on the "route of administration," "excipients in the formulation," "the viscosity of the formulation," "the presence of surfactants in a liquid formulation," "etcetera." A3129 (78:5-79:8). Dr. Berkland—Par's expert—likewise testified that multiple factors, including particle size, concentration, and other ingredients, can affect the pharmacokinetic properties that a specific formulation exhibits. *See* A3237-38 (23:11-25:15). He explained that the patent "discloses a method to create an oral suspension formulation," which includes "adjusting ingredients like surface stabilizers, surfactants, other agents that are present that might help dissolve the

drug in the suspension." A3237 (24:25-25:4). In addition to particle size, one could "adjust the formulation by adding more surfactant, adding some more of this ingredient, hydroxypropylmethylcellulose, which is known to help solubilize poorly water-soluble drugs and dry that drug into solution to achieve the claimed benefits." *Id.* (25:5-13). Dr. Fleckenstein—Par's expert—discussed a study involving a nanoparticulate formulation of a different drug that **increased** the food effect. A3168 (21:25-23:1).

The fed-fasted variability of a particular formulation can be greatly influenced by particle size, but it can also be significantly influenced by other factors. In contrast to *In re Kao*, 639 F.3d 1057 (Fed. Cir. 2011), *Kubin*, 561 F.3d at 1357, and *Alcon*, 687 F.3d at 1369, the '576 patent specification makes clear that the claimed pharmacokinetic properties are not inherent but result from the adjustment of numerous variables. The patent itself states that "**[i]f** the liquid dispersion medium is one in which the nanoparticulate megestrol has very low solubility, the nanoparticulate megestrol particles are present as suspended particles" and the "smaller the megestrol particles, the higher the **probability** that the formulation will exhibit the desired pharmacokinetic profile." A8213 (12:57-62). But inherency requires necessary conditions and not probabilities.

In addition, the inventors described and claimed progressively narrower limitations—*e.g.*, "no substantial difference" in fed/fasted variability, variability of

"less than about 100%," variability of "less than about 60%"—precisely because many different nanoparticulate formulations with different pharmacokinetic properties can be made. A8211-12 (8:57-58, 9:4-9). Some of the preferred formulations **disclosed in the patent specification** fail to achieve some of the dependent claim limitations the court summarily held inherent. For example, formulations A and C in Table 12 do not result in the most preferred fasted-state C_{max} of 700 ng/ml as required by claims 12, 13, 26 and 27. *See* A8228 (Table 12, Formulations A & C (C_{max} of 410 and 650 ng/ml respectively)). The patent itself, therefore, proves that the limitations in these narrower claims are not inherent properties of nanoparticulate formulations of megestrol acetate. Likewise, for the fed/fasted variability limitations (less than 100%, less than 60%, no substantial difference), the most preferred formulations span the range of 8-55%,[6] but the specification envisions formulations with up to 100% variability still falling within the broadest claims. If 100% variability is possible, then the narrower claims, *e.g.*, 60% in claim 5, cannot be inherent. For example, the patent presents results from a dog study that calculate 71% to 84% fed/fasted variability. A8221 (Tables 2 &

[6] Dr. Fleckenstein's chart, A7822, demonstrating embodiments of the invention with fed/fasted variability ranges of 8-55% shows that certain claimed embodiments can result in less than a 60% food effect, but those were all embodiments created by the inventors to solve the food effect they discovered. That does not show that eliminating the food effect is inherent and necessarily present in all nanoparticulate formulations.

3) (*see* note 1, *supra*, for calculation formula). Accordingly, claims 5, 12, 13, 26 and 27 are independently valid.

Moreover, TWi's experts did not testify that the claimed pharmacokinetic parameters were inherent, but instead testified that they were not even enabled outside of a narrow range. A3119 (38:17-39:24) (The patent "shows us only how to obtain improved fed/fasted, the improved fed/fasted property that's claimed with particles in the 100 to 400 nanometer range."); *see also* A27690 ("None of the literature available shows the food effect for megestrol formulations with a D^{90} particle size greater than 400nm."); A27820 ("[A] skilled artisan would not know how to obtain the claimed reduction in fed/fasted variability across the claimed particle size range—an effective average particle size of 0 to 2200nm."). TWi's enablement defense lacked merit because a person of ordinary skill, given the teachings of the '576 patent, is able to practice the full scope of the invention without undue experimentation. But TWi's admissions contradict any assertion that every time nanoparticulate technology is applied to megestrol acetate, the claimed limitations will always, invariably result.

The district court did not address any of this evidence, and it glossed over all of the variables other than particle size that can affect a formulation's pharmacokinetic properties. TWi has not shown by clear and convincing evidence that **all** nanoparticulate formulations of megestrol acetate will eliminate the

"substantial difference" between the fed and fasted states (claim 1), or that they will all result in a difference in the C_{max} between the fed and fasted states of less than 100% (claim 4), or that they will all result in a difference in the C_{max} between the fed and fasted states of less than 60% (claim 5). *See* A8228-29 (42:55-44:43).

On the issue of inherency, this case is similar to *Allergan*, 726 F.3d 1286. In *Allergan*, this Court explained that it could not find a claim obvious based on inherency because "[t]he evidence of record does not establish that the dose reduction 'from 3 to 2 times a day without loss of efficacy' limitation is an inherent property or a necessary result of the administration of 0.2% brimonidine and 0.5% timolol in a single composition. Of course, it **may** be true that the mere administration of 0.2% brimonidine and 0.5% timolol twice daily in any fixed combination formulation inherently produces the claimed result. Alternatively, it **may** also be true that only certain fixed-combination formulations produce this result." *Id.* at 1294 n.1. Likewise here, TWi presented no evidence that every nanoparticulate formulation will satisfy the food-effect limitations.

The district court's misapplication of the inherency principle greatly expands the doctrine, and will severely limit patentability in the pharmaceutical industry. Inherency is usually applied to the anticipation defense because it does not matter for anticipation whether the inherent property was known. This Court has long held that "[i]nherency and obviousness are distinct concepts." *Kloster Speedsteel*

AB v. Crucible Inc., 793 F.2d 1565, 1576 (Fed. Cir. 1986). "That which may be inherent is not necessarily known," and "[o]bviousness cannot be predicated on what is unknown." *Rijckaert*, 9 F.3d at 1534 (quotation marks and citation omitted). "[A] retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." *Id.*

Accordingly, this Court has applied the inherency principle in the obviousness context only in limited circumstances. In *Santarus, Inc. v. Par Pharmaceutical, Inc.*, the asserted '885 patent claims issued from a continuation-in-part application of the cited '737 patent, which qualified as prior art "[d]ue to breaks in the chain of priority." 694 F.3d 1344, 1347-48, 1352 (Fed. Cir. 2012). Thus, the '737 patent disclosed the formulation in the later-issued '885 patent claims, which merely added blood serum concentrations. *Id.* at 1353-54. The Court found those claimed serum concentrations inherent because "merely by testing and claiming an inherent property" did not make the previously-disclosed formulation patentable. *Id.* at 1354.

Similarly, in *Kao*, the patent holder added a limitation claiming an inherent pharmacokinetic property to a previous formulation. 639 F.3d at 1070. The specification explained that "the claimed 'food effect' is an inherent property of oxymorphone itself, present both in controlled release"—the invention at issue—"and immediate release formulations of that drug." *Id.* The court specifically

relied on *King Pharmaceuticals, Inc. v. Eon Labs, Inc.*, which held that "'merely discovering and claiming a new benefit of an **old process** cannot render the process again patentable.'" 616 F.3d 1267, 1275-76 (Fed. Cir. 2010) (citation omitted).

The district court appears to have erroneously construed *Santarus* and *Kao* to mean that all pharmacokinetic properties are always "inherent." But in contrast to these cases, no prior-art reference in this case disclosed any nanoparticulate formulation of megestrol acetate, and no record evidence shows that any and every formulation made following the prior art would inherently solve the previously-unknown food-effect problem. This is not a situation where the patent holder merely tested and claimed an inherent property of an existing formulation of the drug.

3. The District Court's Finding Of "Other" Motivations Is Clear Error

Even putting aside the district court's legal errors discussed above, the district court committed clear error in finding that viscosity and interpatient variability would have motivated a skilled artisan to reformulate megestrol acetate using nanoparticulate technology. That error provides an independent basis for setting aside the district court's obviousness ruling.

The district court's analysis of both motivations suffers from two fatal flaws. First, the evidence at trial did not establish that viscosity and interpatient variability

were **appreciated** in the art **at the time of the invention** to be problems with the existing Megace OS formulation. Second, the evidence did not establish that nanotechnology would have been considered a preferred approach to address these problems. More generally, the court failed to objectively look at the art as a whole to evaluate what options were available to a skilled artisan. Instead, the court used hindsight to hunt for a motivation where there was none.

a. No Prior Art Described Viscosity As A Problem, Nor Suggested Nanotechnology As A Preferred Solution

No prior art reference stated that viscosity (or dose volume) was a problem with Megace OS, and the district court cited none. TWi's only trial evidence regarding viscosity referred to statements in the '576 patent itself. *See* A3009 (33:3-11); A3063 (52:4-8); A3091 (26:7-30:22); A3116-17 (26:2-29:16). The district court first erred by relying on statements in the patent itself. A29. The court also relied on Dr. Liversidge's testimony that Megace OS was administered in a half-cup dose. *Id.* But these issues became "problems" only after the invention provided a better alternative. Given the critical condition of these patients, there is no evidence that clinicians **before** the invention were concerned with viscosity. In the nearly ten years Megace OS was available prior to the '576 invention, not a single publication referenced either a viscosity or dose volume problem. The district court also erroneously relied on Par's after-the-fact

marketing materials, which "emphasized reduced volume and reduced viscosity as benefits of Megace ES." *Id.*; *see* A3252 (81:18-83:20).

"Obviousness may not be established using hindsight or in view of the teachings or suggestions of the inventor." *Para-Ordnance Mfg., Inc. v. SGS Importers Int'l, Inc.*, 73 F.3d 1085, 1087 (Fed. Cir. 1995); *see also Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight."). The district court's reliance on the patent's disclosure of the advantages of the invention, expert testimony regarding the same, and post-invention marketing materials is prohibited hindsight.

Second, the court erred in its motivation finding because TWi did not show that viscosity would have motivated one to use nanotechnology. The court's **only** evidence relating decreased viscosity to nanotechnology was Dr. Fleckenstein's testimony—in response to questioning from the court that was **not linked** to the pre-2002 timeframe—that the nanoparticulate formulation "would be expected to" help with viscosity. A29; *see* A3183 (83:6-23). Immediately after that exchange, Dr. Fleckenstein explained that one of ordinary skill in the art **in 2002** seeking to solve a viscosity problem would have reformulated the drug as in the Brubaker patent. A3183 (84:1-9). In that patent, he explained, the inventor "was changing all of these things, like pH and the surfactants, and that sort of thing, **but did not**

change the particle size," even though nanotechnology was known at the time. A3183 (82:3-15).

This testimony does not amount to clear and convincing evidence that viscosity would have motivated skied artisans to reformulate the drug using nanotechnology. This Court "retain[s] plenary review to determine whether, as a legal matter, the evidence satisfies the clear-and-convincing standard of proof." *Cyclobenzaprine*, 676 F.3d at 1069. Here, the evidence plainly does not.

b. No Prior-Art Described Interpatient Variability As A Formulation Problem, Nor Identified Nanotechnology As A Preferred Solution

The district court's reliance on "interpatient variability" of Megace OS was error for the same two reasons. First, no prior art taught that interpatient variability was a problem associated with the existing formulation. A30-31. The prior art reported that the observed variability was caused by the different complications in the HIV/AIDS patients being studied—they never even suggested it was any problem with the Megace OS formulation, including the drug's bioavailability. Graham concluded that enteropathy (an HIV-related condition where the gut does not function, A3213 (31:13-14)); achlorhydria (the absence of acid secretion in the stomach, A3173 (41:5-6)); other factors that "alter the GI [gastrointestinal] physiology in these [HIV/AIDS] patients," *id.* (41:7-8), *e.g.*, diarrhea, gas, bloating, abdominal pain, opportunistic infections, malabsorption, A3213 (30:24-

31:24); and interactions with concurrent HIV/AIDS medications likely caused the variability, A15932-33; A12. Oster reported that the variability was related to the degree of wasting in the patient. A6069; A13.

The constellation of specific complications these references reported varies widely among HIV/AIDS patients and cannot be addressed by a formulation change. A3173 (41:21-42:12). Graham instead recommended dose individualization to address the observed intersubject variability. A15931, 15933. And Oster recommended treating patients earlier, before wasting became severe. A6069. But the district court dismissed these reported conclusions by contemporaneous experts as "nothing more than speculat[ion] as to the underlying causes" of variability. A13. That was error.

Second, the court also erred because the evidence did not establish that nanotechnology would have been considered a preferred approach to address interpatient variability. According to the court, the facts that reducing particle size "affects dissolution rates" and "reducing particle size had improved the bioavailability of megestrol acetate before" would have "suggested to a person skilled in the art that the remaining variability in absorption levels in some patients may be due to bioavailability problems and that nanotechnology could address those issues in some patients." A31. To support this conclusion, the court relied only on the inventors' own work and on a general nanotechnology reference

(Müller) that noted nanoparticles' "adhesion process" could reduce "erratic absorption" and was "little affected by the nutritional status of the patient." A23-24. Unlike Graham and Oster, Müller was not addressing Megace OS, the unique and varied conditions of HIV/AIDS patients, or any of the pertinent issues faced by a person of ordinary skill in 2002.

Further, even if a skilled artisan had been motivated to try to address interpatient variability using nanotechnology, they would have quickly found that Graham and Oster had correctly attributed the cause to the patient population rather than the formulation. The Wanke study showed that while Megace ES did solve the food-effect problem, the problem of interpatient variability persisted. *See* A6079 (Table 2: Megace ES weight gain 5.4 kg **± 5.32 kg**; Megace OS weight gain 3.5 kg **± 4.03 kg)**.

c. The Court Improperly Used Hindsight To Hunt For Motivation Where There Was None

The district court's motivation analysis was also legally flawed in that it failed to undertake the required objective inquiry, from the perspective of a hypothetical ordinarily skilled artisan in 2002—looking at the prior art as a whole. Viewed from the legally proper perspective (a hypothetical ordinarily skilled artisan in 2002), the complexity of the issues facing such a hypothetical artisan precludes a finding of obviousness.

As discussed below, *see infra* at 53-54, Graham taught that Megace OS has a highly unusual pharmacokinetic/pharmacodynamic ("PK/PD") relationship: more drug absorbed (AUC) did not lead to more weight gain, slower absorption improved results, and faster absorption resulted in no weight gain. On top of that complexity, absorption is a complex, multifactorial process and the effect of altering the release profile is notoriously unpredictable. *See* A3151-52 (39:8-41:6); A3167 (17:1-18:10); A6024-28.

Nanotechnology—with only one drug FDA-approved—had no established body of evidence to support the idea that a successful formulation was even likely, and at a minimum promised to be a lengthy development effort. A3146 (17:11-18:23). The court failed to meaningfully address the many other, more established options available to address viscosity or interpatient variability. *See* A3235 (13:17-16:7). Indeed, Elan's marketing materials emphasized that the one approved nanoparticulate product was a tablet that replaced an earlier "oral solution" formulation, providing patients "with more convenient administration and storage." A15633. The court never considered whether this would motivate a skilled artisan to pursue a nanoparticulate tablet rather than the claimed oral suspension. Nor did the court consider medically treating the enteropathy, achlorhydria, or other conditions Graham said were responsible for the variability. The court's reliance on the "simplicity" reported in some references for the process

of creating nanoparticles fails to account for the real complexity of developing a new, finished dosage form using new technology, and the lack of predictability of the result.

The error in the district court's obviousness analysis is underscored by this Court's decision in *Leo*, 726 F.3d 1346. In *Leo*, this court reversed an obviousness determination by the Board of Patent Appeals. *Id.* at 1348. The patentee discovered that it was difficult to create a storage-stable formulation containing both vitamin D and corticosteroids, and solved the stability problem. *Id.* at 1349. As in this case, the inventor amended the claims by adding a "wherein clause" to make storage stability an explicit limitation. *Id.* at 1350. The Board found that a combination of three references rendered the claims obvious, even though the prior art did not teach the main benefit of the patent—a storage-stable combination of the drugs. *Id.* at 1350-52. The Board nonetheless concluded that "'the reason for utilizing the solvent does not have to be the same reason [the solvent] was employed by the inventors.'" *Id.* at 1352 (citation omitted).

This Court reversed, finding that the Board "brush[ed] aside the storage stability issue" and "collaps[ed] the obviousness analysis into a hindsight-guided combination of elements." *Id.* at 1354. One prior-art reference had been around for 22 years, but no one had sought to improve it with Vitamin D. Another reference "even targeted the precise side effects that the Board believed would

have motivated the addition of a vitamin D analog to Turi's corticosteroid composition, yet [the reference] did not seek to improve Turi by adding vitamin D." *Id.* at 1355. So too here. The 2002 Brubaker reference targeted the reformulation of Megace OS to address "pharmaceutical elegance," but it did not suggest using nanotechnology even though the Liversidge references were published in 1992-1995. A3183 (82:3-84:9). The district court dismissed Brubaker because "an inventor focused on creating a generic formulation" would not have changed particle size, "an underlying structural aspect" of the product. A30. But that finding just shows that the obvious path was to pursue a generic formulation with the same particle size, because there was no perceived benefit to a "structural" reformulation.

Leo compels the conclusion that the district court's obviousness analysis was fundamentally flawed. In *Leo*, ordinary artisans would not have been motivated to create a storage stable solution because they "would not have recognized the problem." 726 F.3d at 1357. Likewise, here, ordinary artisans would not have been motivated to create a formulation with the claimed food-effect parameters because they did not know the food-effect problem existed. And, as in *Leo*, the more general motivations identified above do not suffice.

The court below appeared to adopt the alternative motivations because it drew an adverse inference from the fact that the inventors did not start their

research intending to solve the then-unknown food effect. A27 n.18. That is a fundamental error. "Patentability shall not be negated by the manner in which the invention was made." 35 U.S.C. § 103. Indeed, "an invention can often be the recognition of a problem itself." *Leo*, 726 F.3d at 1353. That the inventors discovered a surprising problem while doing basic research supports, rather than detracts from, patentability.

4. The Prior Art Taught Away From Using A Nanoparticulate Megestrol Acetate Formulation

Separate from the other errors already identified, the district court's obviousness finding should be reversed because the court erroneously dismissed evidence that the prior art taught away from the invention. "A reference that properly teaches away can preclude a determination that the reference renders a claim obvious." *In re Mouttet*, 686 F.3d 1322, 1333 (Fed. Cir. 2012); *see also KSR*, 550 U.S. at 416 ("[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious."). *Graham* taught squarely and directly away from the claimed invention by teaching that more rapid absorption would lead to less weight gain. *See* A15932-33; A3179 (65:10-66:10).

The results in *Graham* were striking. Patients who showed "more rapid absorption" (which *Graham* called a "2-compartment" model) gained no weight—indeed, they lost 0.2 kg on average. A15932-33. Patients who had "slower

[absorption], resulting in more sustained plasma megestrol concentrations" (which Graham called a "1-compartment" model) gained an average of 3.6 kg (almost 8 pounds). *Id.* But nanotechnology was taught to **cause more rapid absorption** of drugs, A14956 (Figure 2), the precise effect *Graham* said did not work. TWi's expert agreed that "more rapid absorption" was expected from nanotechnology. A3123 (54:8-12). Dr. Fleckenstein explained that nanoparticulate formulations "would have more rapid absorption, and this would have been associated with a poor outcome from the basis of the Graham article." A3179 (65:10-66:10). Further, in contrast to the typical expectation when taking a drug (*e.g.*, Advil) that two tablets will provide a greater effect than one tablet, A3170 (30:8-15), Graham taught that simply making megestrol acetate more bioavailable would not make it more effective, *id.* (29:25-31:8). Rather, Graham indicated that megestrol acetate exhibited a threshold effect, where efficacy depended on the number of hours per day spent above a threshold concentration of 300 ng/mL:

> [T]his trend revealed a statistically significant relation between weight gain and the percentage of the 24-h dosing interval that plasma megestrol concentrations exceeded a 300-ng/ml threshold (Fig. 2). In contrast, megestrol AUC (a measure of total drug exposure in vivo) was not correlated with weight gain ….

A15933; *see also* A3173-74 (42:21-43:4, 46:18-47:6).

The pharmacokinetic/pharmacodynamic relationship that Graham taught "would really discourage pursuing a nanoparticulate approach," A3158 (66:10-12),

because it taught that rapid absorption is undesirable, A3173 (43:15-44:7). *See Cyclobenzaprine*, 676 F.3d at 1067-73 (reversing obviousness determination because of district court's clear error in evaluating PK/PD relationship). To obtain more sustained plasma drug concentrations above a threshold, a person of ordinary skill would use a sustained-release dosage form. A3123 (55:12-19). Dr. Fleckenstein testified that Graham would suggest an extended-release dosage form and teach away from a nanoparticulate dosage form. A3173-74 (42:13-47:13). TWi's expert, Dr. Beach, never responded to Dr. Fleckenstein's teaching away testimony.

But the district court nonetheless rejected this uncontested evidence—inventing an argument that neither TWi nor its experts made. *See* A34. According to the district court, "[n]anoparticles were known to increase absorption levels and were associated with longer dose retention, (*See* DTX 177 at 2), features that ostensibly would contribute to higher concentration levels for longer time periods." *Id.*

The district court's only citation for this *sua sponte* conclusion was a printout from an Elan website that nanocrystal particles "**may** then enable the following differentiated advantages ... Longer dose retention in blood and tumors for **some** compounds." A15634. This equivocal statement about "some compounds" says **nothing** about the compound at issue: megestrol acetate.

Furthermore, the cited statement says nothing about oral suspensions. It appears to relate to **injectable** dosage forms, *id.*; *see also* A14958, and relates to the potential for nanoparticles of cancer drugs to accumulate in tumors when directly injected, A3069 (76:12-14). The behavior of an injected suspension of drug **particles** has absolutely nothing to do with pharmacokinetics following oral administration. A3175-76 (52:11-53:3). Following oral administration, the drug enters the blood stream only after it **dissolves** into solution and passes through cell membranes in a process that involves numerous complicating factors. A3151-52 (39:8-41:6). Since an orally-administered drug enters the bloodstream in **solution**, there is no basis to conclude (and no evidence in the record) that a nanoparticulate oral dosage form—despite its more rapid absorption—would somehow be expected to simultaneously have "more sustained plasma megestrol concentrations." A15932.

Pharmacokinetics of orally-administered drugs typically follow a standard pattern: faster absorption leads to faster metabolism and elimination as described by the half-life and elimination rate constant. Consistent with this expectation, the '576 patent shows that the half-life ($t_{½}$) and elimination rate constant (K_{el}) of megestrol acetate were the same for Megace OS, *see* A8228 (Tables 12 & 13, Treatment B), as for the nanoparticulate formulations of the invention (Treatments A, C and D). A nanoparticulate formulation is not an extended-release technology.

B. The District Court Improperly Dismissed Objective Evidence Of Nonobviousness

Courts must also consider objective evidence of nonobviousness "before making an obviousness determination." *Cyclobenzaprine*, 676 F.3d at 1079. The party challenging validity has the burden of establishing invalidity, and it is error to "shift[] the burden of persuasion to" the patent owner to prove nonobviousness. *Id.* at 1078, 1075. Objective indicia of nonobviousness "play a critical role" and "are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements." *Leo*, 726 F.3d at 1358 (quotation marks and citation omitted). Here, among other things, Par presented strong evidence of unexpected results and that the invention satisfied a long-felt and unmet need. The district court erroneously dismissed this evidence, which in itself was sufficient to defeat TWi's obviousness challenge.

1. There Was Significant Evidence Of Unexpected Results

When a "claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected," that undermines a showing of obviousness. *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quotation marks and citation omitted). "The basic principle behind this rule is straightforward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). It

"applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results." *Id.*

Here, the claimed invention surprisingly eliminated a previously unknown food effect. *See* A10-20 (food effect was unknown). Both the discovery of the food effect and the solution were unexpected. This double showing that the invention has unexpected properties significantly undermines TWi's obviousness defense.

The district court acknowledged that the food effect was unknown, but dismissed the unexpected results on the ground that they were not related to the motivations to combine that the court had identified. In the court's view, "[t]he fact that the use of nanotechnology may have surprisingly solved" the food effect did not undermine the court's obviousness finding because that finding was based on "motivations in the art other than fed-fasted variability." A37. That was legal error.

The district court collapsed two separate inquiries—whether there is a motivation to combine prior-art elements and whether the combination yields unexpected results. An unexpected result need not flow from the motivation to combine to be significant. Indeed, as a matter of logic, something that solved the problem that the motivation identified would not be unexpected. An unexpected result is not **less** surprising and more obvious because it is unrelated to the

motivation to combine. Under the district court's reasoning, if prior art supplied a motivation to combine certain kinds of drugs to treat a headache, but the inventor discovered that a particular combination unexpectedly cured multiple sclerosis, those unexpected results would be irrelevant and the invention unpatentable. That is wrong. The Supreme Court explained in *KSR* that "[t]he combination of familiar elements according to known methods is likely to be obvious **when it does no more than yield predictable results**." 550 U.S. at 416. But the opposite is also true: a combination of elements that does **more** than yield predictable results is **not** obvious.

This Court has relied on unexpected results that were unrelated to the motivation to combine the prior art references. For example, in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, this Court found "powerful unexpected results" of anticonvulsive activity of "particular importance" when evaluating a drug that the alleged infringer argued was obvious because "a person of ordinary skill in the art faced with finding a diabetes drug" would "necessarily" have designed the drug. 520 F.3d 1358, 1363-64, 1365 (Fed. Cir. 2008). And in *Procter & Gamble*, this Court approved the district court's conclusion that the unexpected results of high potency and low toxicity would have rebutted a finding of obviousness based on a motivation from prior art to develop a drug that effectively treated osteoporosis. 566 F.3d at 993, 997. Just as in these cases, the

district court should not have rejected Megace ES's unexpected results in solving the food effect merely because it had found an unrelated motivation in the art.

Contrary to the district court's reasoning, *Allergan* does not demand a different result. The panel in *Allergan* did not completely discount the unexpected results because they were unrelated to the motivation to combine. Instead, the court simply "d[id] not find that these unexpected results [were] sufficient to outweigh the other evidence of obviousness as to these formulation claims." 726 F.3d at 1293. The district court gave *Allergan* an overbroad reading—holding that an unexpected result (no matter how significant) cannot as a matter of law overcome an unrelated motivation to combine (no matter how weak). That would gut the "critical role," *Leo*, 726 F.3d at 1358, of the unexpected results inquiry.

Had the district court properly considered Par's objective evidence of the unexpected food effect, this objective evidence of nonobviousness would have overcome the court's obviousness determination. Megace OS's food effect was completely unappreciated in the prior art. *See* A10-20. The invention's substantial elimination of that effect, therefore, was different in kind and not merely in degree, making it an unexpected result that is probative of nonobviousness.[7] *Galderma*

[7] In a footnote, the district court stated that the improvements "do not appear to be more than what might be predicted given the known improvements in efficacy associated with nanotechnology," and suggested the result was merely of degree.

Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 739 (Fed. Cir. 2013), *petition for cert. filed*, No. 13-1350 (U.S. May 7, 2014).

The solution was drastic. The patented invention reduced the fed/fasted difference in C_{max} from a range of 629-787% to a range of 8-55%. A3165 (11:5-8); A3169 (25:13-26:6). As Dr. Fleckenstein testified, the patented invention "really dramatically decreased the food effect," which was "among the largest that [he had] seen for other drugs." *Id.* (28:11-25). For the first time, the patented invention allowed megestrol acetate to be administered "without regard to meals," A5957, which was a significant benefit to patients that were having trouble eating.

Moreover, courts have long recognized that where an inventor is the first to discover the source of a known problem, that discovery supports the conclusion that the solution is nonobvious. *Eibel Process Co. v. Minnesota & Ont. Paper Co.*, 261 U.S. 45, 67-68 (1923); *In re Sponnoble*, 405 F.2d 578, 585 (C.C.P.A. 1969) ("[A] patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified."); *Leo*, 726 F.3d at 1353 ("[A]n invention can often be the recognition of a problem itself."). Where, as here, the problem **itself** was not known to exist, that

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A37 n.20. But substantially eliminating a more than 600-700% food effect is more than a general improvement. As in *In re Chupp*, Megace ES is "unexpectedly superior in one of a spectrum of common properties," which "can be enough to rebut a *prima facie* case of obviousness." 816 F.2d 643, 646 (Fed. Cir. 1987).

unexpected problem is powerful evidence that the unexpected solution embodied in the invention is not obvious. Given that "there is no evidence of record that a person of ordinary skill in the art at the time of [Par's] invention would have expected the problem ... to exist at all, it is not proper to conclude that the invention which solves this problem ... would have been obvious." *In re Nomiya*, 509 F.2d 566, 572 (C.C.P.A. 1975). Par's objective evidence of the unexpected food effect and its significance thus alone compels a finding of non-obviousness.

2. There Was Significant Evidence Of Long-Felt Need

Objective evidence of a long-felt and unmet need "is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *Cyclobenzaprine*, 676 F.3d at 1082. There was significant evidence of a long-felt and unmet need here.

At trial, Par presented evidence that the claimed invention addressed the long-felt need of promoting greater weight gain in HIV/AIDS patients. Since AIDS was first diagnosed, there have been "an extraordinary number of patients who were experiencing devastating weight loss," which was "contributing to death or causing death in patients who had the HIV infection." A3217 (47:3-10). There were few treatments and, although Megace OS did result in weight gain, it did not return patients to premorbid weight. *Id.* (47:11-13). The invention satisfied that

need by helping HIV/AIDS patients gain more weight, more quickly. *See supra* at 7-9. Dr. Wanke, who has treated numerous patients suffering from these symptoms, testified: "I believe the fact that [Megace ES has] resulted in more substantial weight gain than was seen in patients with Megace OS that it plays a very predominant and important role in treatment of weight loss and HIV infection." A3214 (33:14-17).

The district court rejected this evidence because only some of the asserted claims are limited to HIV/AIDS patients. A38. And, for those claims, the court rejected the evidence because Dr. Wanke's publication, A6077-78, stated only that the "'use of the [Megace ES] formulation **may** be preferable to [Megace OS],'" A39 (alterations in original) (quoting A6086).

The district court's reason for rejecting the significant evidence of the long-felt and unmet need in HIV/AIDS patients was erroneous. The court rejected **all** of the evidence on the basis of one statement in Dr. Wanke's study, which is in no way inconsistent with an unexpected result. The court disregarded her **actual testimony**, which was based not only on the exhibit but also on her own experiences in treating patients and consulting. Moreover, the court did not address her testimony that the study showed "that the individuals who were randomized to receive Megace ES gained a substantial, significantly different, significantly greater amount of weight than the individuals who were randomized

to receive Megace OS." A3215 (38:7-10). She further explained that the difference in weight gain shown in the study was "quite clinically meaningful" both because "it leads to a greater degree of weight gain" and "there's a more rapid weight gain early on," which results in patients being "much more likely to continue to take the preparation through the suggested 12-week course." A3216 (41:16-23); *see also id.* (42:10-43:8).

In a footnote, the district court dismissed the study on the ground that the "mean weight gain between the two formulations was only ever, at most, two kilograms." A39 n.22. But two kilograms would be three percent of an average 70 kilogram person (and a much higher percentage of an anorexic HIV patient), and Dr. Wanke testified that "differences as small as 3 percent or 1 percent can be associated with long term disadvantageous outcomes." A3216 (42:3-5).

For all of these reasons, the district court's finding that there was not a long-felt and unmet need was clearly erroneous. The significant evidence of a long-felt and unmet need undermines the court's prima facie conclusion of obviousness—especially when combined with the evidence of unexpected results.

CONCLUSION

For the foregoing reasons, the judgment of the district court should be reversed and the case remanded for further proceedings.

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DECLARATION OF AUTHORITY PURSUANT TO FEDERAL CIRCUIT RULE 47.3

Pursuant to Rule 47.3(d) of the Rules of the Unites States Court of Appeals for the Federal Circuit, I, Daniel G. Brown, of Latham & Watkins LLP, hereby swear under penalty of perjury pursuant to 28 U.S.C. § 1746 that Maryellen Noreika, Counsel for Plaintiff-Appellant Alkermes Pharma Ireland Limited, has authorized me to sign the Opening Brief for Appellants on her behalf.

Executed on: June 2, 2014

/s/ Daniel G. Brown
Daniel G. Brown

CERTIFICATE OF SERVICE

I certify that on June 2, 2014, the foregoing OPENING BRIEF FOR APPELLANTS was filed electronically using the CM/ECF system, which will send notification of such filing to counsel of record.

/s/ Daniel G. Brown
Daniel G. Brown

CERTIFICATE OF COMPLIANCE WITH
FEDERAL RULE OF APPELLATE PROCEDURE 32(A)

Counsel for Appellants, Par Pharmaceutical, Inc., and Alkermes Pharma Ireland Limited hereby certify that:

1. This Brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B): The Brief contains 13,870 words (as calculated by the word processing system used to prepare this brief), excluding the parts of the Brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This Brief complies with the type face requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). The Brief has been prepared in proportionally spaced typeface using Microsoft Word in 14 point Times New Roman style font.

Dated: June 2, 2014

Respectfully submitted,

/s/ Daniel G. Brown
Daniel G. Brown

ADDENDUM

Addendum Pursuant to Rule 28(a)(12) and Federal Rule of Appellate Procedure 28(f)

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

PAR PHARMACEUTICALS, INC. and ALKERMES PHARMA IRELAND LTD.	:	
v.	:	Civil No. CCB-11-2466
TWI PHARMACEUTICALS, INC.	:	

ORDER

For the reasons stated in the accompanying memorandum, it is hereby ORDERED that:

1. TWi Pharmaceuticals, Inc.'s Motion in Limine (ECF No. 167) is **DENIED** as moot;
2. TWi Pharmaceuticals, Inc.'s Motion to Seal its Pretrial Brief (ECF No. 170) is **GRANTED**;
3. Par Pharmaceuticals, Inc. and Alkermes Pharma Ireland Ltd.'s Motion to Seal their Pretrial Brief (ECF No. 172) is **GRANTED**;
4. TWi Pharmaceuticals, Inc.'s Motion to Seal its Post-Trial Brief (ECF No. 200) is **GRANTED**;
5. The asserted claims of the patent-in-suit are invalid as obvious in light of the prior art;
6. Judgment is entered in favor of TWi and against the plaintiffs;
7. The Clerk shall **CLOSE** this case; and
8. The Clerk shall send copies of this Order and the accompanying Memorandum to counsel of record.

February 21, 2014
Date

/s/
Catherine C. Blake
United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

PAR PHARMACEUTICALS, INC. and ALKERMES PHARMA IRELAND LTD.	:	
v.	:	Civil No. CCB-11-2466
TWI PHARMACEUTICALS, INC.	:	

MEMORANDUM

Plaintiffs Par Pharmaceuticals Inc. and Alkermes Pharma Ireland, Limited (collectively, "Par") filed this action against TWi Pharmaceuticals, Inc. ("TWi") alleging infringement of U.S. Patent 7,101,576 ("the '576 patent"). The patent relates to Par's Megace ES medication, a nanoparticulate formulation of megestrol acetate used to treat anorexia, cachexia, and unexplained weight loss in patients with HIV and AIDS. After this court's summary judgment order, and prior to trial, the parties stipulated that TWi's generic version of Megace ES would infringe the asserted claims of the '576 patent, leaving before this court only TWi's defense that the '576 patent is invalid and its claim that Par Pharmaceuticals, Inc. does not have standing to bring suit as co-plaintiff. A five-day bench trial to determine the remaining claims was held in October 2013. After hearing the evidence and considering the post-trial briefs, the court concludes that the '576 patent was obvious, and thus invalid.[1] Pursuant to Federal Rule of Civil Procedure 52(a), the following memorandum constitutes the court's findings of fact and conclusions of law.

BACKGROUND

In 1993, Bristol Meyers Squibb ("BMS") began marketing Megace OS, an oral

[1] Because the court finds the claims are obvious, it does not need to decide whether Par Pharmaceuticals, Inc. has standing, whether the claims of the '576 patent are enabled, or whether the patent claims patentable subject matter.

suspension of micronized megestrol acetate,[2] to treat anorexia and cachexia in AIDS patients. The drug was a medical and commercial success. In fact, the FDA subsequently approved five abbreviated new drug applications ("ANDAs") for generic versions of Megace OS, including one submitted by Par. According to TWi, by 2005, Par had the majority of the generic Megace OS market, with approximately $25 million in annual sales.

During experimentation with reformulating the drug to reduce the particle size of the megestrol acetate to the nanoparticulate range (using Alkermes's already patented "NanoCrystal" technology), the inventors of the '576 patent discovered, "surprisingly," according to Par, that BMS's Megace OS exhibited low bioavailability when administered to a patient without food and much higher absorption when administered with food. Par asserts that this "strong food effect" was previously unknown and that it is a significant weakness in Megace OS because the target patients of the drug are individuals suffering from conditions with low appetites, thus making it unlikely the drug can be administered in a sufficiently fed state. The '576 patent inventors discovered, however, that their new nanoparticulate formulation resulted in dramatically improved bioavailability in the fasted state and reduced the absorption difference between the fed and fasted states. The '576 inventors filed for patent protection for this new formulation in 2002. The Patent Office rejected the application several times because it deemed the claimed invention obvious in light of the prior art. (*See, e.g.*, Pl.'s Trial Ex., [hereinafter PTX], 359.) After Par amended its application to highlight the reduced fed-fasted effect, (Def.'s Trial Ex., [hereinafter DTX], 248), the Patent Office eventually granted the application and issued the patent in 2006.

The '576 patent claims a method of treating wasting in humans. Claim 1 is representative

[2] Megestrol acetate is a synthetic derivative of the naturally occurring steroid hormone progesterone.

of the asserted independent claims:

> "A method of increasing the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass, comprising administering to the human patient a megestrol formulation, wherein:
>
> (a) the megestrol acetate formulation is a dose of about 40 mg to about 800 mg in about a 5 mL dose of an oral suspension;
> (b) the megestrol acetate formulation comprises megestrol particles having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer associated with the surface of the megestrol particles; and
> (c) the administration is once daily;
> wherein after a single administration in a human subject of the formulation there is no substantial difference in the C_{max} of megestrol when the formulation is administered to the subject in a fed versus a fasted state,
> wherein fasted state is defined as the subject having no food within at least the previous 10 hours, and wherein fed state is defined as the subject having a high-calorie meal within approximately 30 minutes of dosing."

(DTX 1 at Claim 1; *see also* Claim 4.) The asserted dependent claims claim the use of the method in treating wasting associated with HIV/AIDS, (*Id.* at Claims 2, 10, 21, 24), various plasma concentration levels, (*Id.* at Claims 5, 7, 12-15, 19, 26-29), and the use of a surface stabilizer, (*Id.* at Claims 16, 17, 30, 31).

Around the same time the '576 patent was approved, the FDA approved Par's New Drug Application for Megace ES, a nanoparticulate megestrol acetate oral suspension that the parties have stipulated embodies the claims of the patent. (Stipulation, ECF No. 174, ¶ 4(a).) Unlike Megace OS, the FDA-approved label for Megace ES states that the drug can be taken "without regard to meals."[3] (PTX 70 at 2.) According to Par, Megace ES has been a resounding

[3] A 2012 version of the Megace OS label does not direct patients to take it with food, only stating, "[t]he effect of food on the bioavailability of MEGACE Oral Suspension has not been evaluated." (PTX 71 at 3, 12.)

commercial success, resulting in more than $600 million in net sales since its launch in 2005.[4]

TWi filed an ANDA seeking FDA authorization to market a generic version of Megace ES. TWi timely notified Par of this filing, and, under 21 U.S.C. § 355(b)(2)(A) (a "Paragraph IV" certification under the Hatch-Waxman Act), asserted that the '576 patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." Par filed suit in September 2011 to block the sale of TWi's generic product on the grounds that it infringed the '576 patent. Par asserts claims 1-2, 4-5, 7, 10, 12-17, 19, 21, 24, and 26-31 against TWi. In defense, TWi argues the asserted claims are invalid because they are obvious in light of the prior art, are not enabled, and do not cover patentable subject matter. TWi also claims Par Pharmaceuticals, Inc. does not have standing.

OBVIOUSNESS

I. Standard of Review

Patents are presumed valid and a party claiming invalidity must prove it by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S.Ct. 2238, 2242 (2011); *In re Cyclobenzaprine*, 676 F.3d 1063, 1068-69 (Fed. Cir. 2012). A patent is invalid for obviousness "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103.

Obviousness is a question of law based on underlying factual findings as to (1) the level

[4] Par pled guilty in March 2013 to misbranding Megace ES, between 2005 and 2009, by marketing it to geriatric patients, although the FDA had approved its use only for patients with AIDS-related anorexia, cachexia, and unexplained weight loss, and for claiming superior clinical efficacy without conducting relevant clinical studies. (*See* Guilty Plea Transcript, DTX 247 at 14:19-16:1.)

of ordinary skill in the art, (2) the scope and content of the prior art, (3) differences between the prior art and the claimed subject matter, and (4) secondary considerations of non-obviousness such as commercial success, long-felt but unsolved needs, and failure of others. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966)). "An invention is not obvious just 'because all of the elements that comprise the invention were known in the prior art.'" *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1335 (Fed. Cir. 2013) (quoting *Power-One,* 599 F.3d 1343, 1351 (Fed. Cir. 2010)). "Generally, a party seeking to invalidate a patent as obvious must demonstrate . . . that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine*, 676 F.3d at 1068-69. "Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Int'l Co.*, 550 U.S. at 418. Further, the court does not have to rely only on teachings directly aimed at the claimed subject matter, but can take into account inferences and creative steps a person skilled in the art would have taken. *Id.* The inquiry is "expansive and flexible," *id.* at 415, and the court is not required to set aside its common sense, *see id.* at 421.

Once the party challenging validity has made out a prima facie case of obviousness, the patentee can offer evidence of objective secondary considerations of non-obviousness, such as commercial success, long-felt but unsolved need, and failure of others. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359-60

(Fed. Cir. 2007). That the defending party can provide such evidence does not, however, shift the burden away from the challenging party. *Pfizer*, 480 F.3d at 1359-60. Further, secondary considerations cannot overcome a strong prima facie showing of obviousness. *Wyers*, 616 F.3d at 1246.

II. Experts

Before continuing with the merits of the case, it is helpful to describe the backgrounds and qualifications of the various experts on whom the parties relied and to whose testimony the court will refer. TWi relied on the testimony of Dr. David Beach, who has a Ph.D in Pharmacy. He was qualified at trial as an expert in pharmaceutics and has over thirty years of experience working in drug formulation and development, including conducting human clinical trials. (DTX 273; Trial Tr. Day 2, Volume 2, [hereinafter Tr. 2:2], at 15:12-14.) Dr. Beach also has specific experience working with nanoparticles. (Tr. 2:2 at 5:24-6:4; 12:20-13:1.) Par introduced testimony from Dr. Lawrence Fleckenstein, who was qualified as an expert in pharmacokinetics, biopharmaceutics, and clinical trial design.[5] (Trial Tr. Day 3, Volume 2, [hereinafter Tr. 3:2], at 31:1-7.) Dr. Fleckenstein has been a professor of pharmaceutical sciences and Director of the Clinical Pharmacokinetics Laboratory at the University of Iowa for over twenty years, where he conducts studies of the pharmacokinetics and bioavailability of drugs in humans. (PTX 180 at 1; Tr. 3:2 at 22:6-23:5.) He also has published numerous papers on pharmacokinetics, (PTX 180 at 2-16), and has taught pharmacokinetics to university students and FDA reviewers, (Tr. 3:2 at 22:3-5; 25:6-19).

[5] Although Dr. Beach was only qualified in "pharmaceutics," he defined the field as "the science behind the whole development of pharmaceutical products," which includes the physical chemistry and chemistry of compounds, the manufacture of compounds into dosages for humans, as well as administration, pharmacokinetics, and pharmacodynamics of drugs. (Tr. 2:2 at 14:15-24.) Accordingly, his area of expertise, as relevant to this case, is essentially similar to that of Dr. Fleckenstein.

Dr. Cory Berkland also testified for Par and was qualified as an expert in pharmaceutical formulations, with specific expertise in pharmaceutical particles and nanoparticles. (Trial Tr. Day 4, Volume 2, [hereinafter Tr. 4:2], at 79:1-8.) He started studying drug particles during his thesis work for his Ph.D in Chemical Engineering and has continued his work in the ten years since receiving his Ph.D. (Tr. 4:2 at 70:25-71:2; 72:25-74:2.) He is currently a professor of Chemical Engineering and Pharmaceutical Engineering at the University of Kansas. (PTX 176 at 1.)

Par also offered testimony from Dr. Christine Wanke, a Professor of Medicine, Director of the Division of Nutrition and Infection, and Associate Chair of the Department of Public Health and Community Medicine at Tufts Medical School. (PTX 184 at 1.) Dr. Wanke was qualified as an expert in the clinical treatment of nutritional and metabolic complications of HIV and AIDS. (Tr. 4:2 at 24:24-25:5.) Her work is focused on nutritional and metabolic complications of HIV and other infectious diseases, and she has experience in conducting clinical trials. (*Id.* at 19:1-8; 20:11-21:2; 21:12-23:14.)

Finally, both parties introduced expert testimony regarding Megace ES's commercial success. Par introduced the testimony of Dr. Walter Vandaele, an economist and managing director of Navigant Economics, who was qualified as an expert in economic, financial, statistical, and general business issues concerning pharmaceutical products. (PTX 226; Trial Tr. Day 5, Volume 1, [hereinafter Tr. 5:1], at 47:21-48:6.) He has over two decades of experience in the economics of the pharmaceutical industry, with specific experience in the area of commercial success of both brand and generic pharmaceutical companies. (*Id.* at 44:5-45:25.) Mr. Charles Boghigian, testifying for TWi, was qualified as an expert in portfolio management, commercialization, marketing, and promotion of pharmaceutical products. (Trial Tr. Day 5,

Volume 2 [hereinafter Tr. 5:2], at 54:19-55:2.) He has over forty years of experience in pharmaceutical sales and marketing, thirty of which were spent with Hoffman-LaRoche, where he started in sales, but moved to managing sales and marketing for entire regions and drug products—including HIV/AIDS treatments—and eventually heading marketing for the company's entire United States drug market. (DTX 311; Tr. 5:2 at 44:16-18; 45:16-50:2; 51:18-52:22.)

III. Level of Ordinary Skill in the Art

The parties' experts—Dr. Beach for TWi and Dr. Fleckenstein for Par—did not appear to disagree materially over the definition of a person of ordinary skill in the art. Both agreed that a degree of some kind—B.S., M.S., or Ph.D.—was necessary in pharmacy, chemistry or chemical engineering, pharmacokinetics, medicine, or pharmacology. (Tr. 2:2 at 37:6-7; Tr. 3:2 at 59:18-20.) Further, both testified that the person's experience would depend on his level of education: those with less education would require more experience. (Tr. 2:2 at 37:10-17; Tr. 3:2 at 59:17-22.) Finally, there was agreement between the experts' testimony that a person skilled in the art would have basic knowledge of how to formulate the relevant drug compounds as well as their physical and chemical properties. (*See* Tr. 2:2 at 37:8-10, 38:6-9; Tr. 3:2 at 59:13-15.) The court agrees with the experts' conclusions regarding the level of education, experience, and knowledge a person skilled in the art would have and sees no significant difference in their definitions. Dr. Fleckenstein testified that a person of ordinary skill also would have basic knowledge of the treatment of weight loss disorders, (Tr. 3:2 at 59:13-16, 61:2-7), and the court will accept this addition.[6]

[6] It does not appear that Par claims this additional element should make any material difference in the court's analysis. (*See* Pl.'s Brief, ECF No. 201, at 7 n.1 (noting TWi's expert's conclusion regarding the matter "was not materially different").)

IV. Scope and Content of the Prior Art

The effective filing date of the '576 patent for the purposes of § 103 is April 12, 2002, the date of the first provisional application filed by the inventors. *See* 35 U.S.C. §§ 103, 119(e)(1). Thus, relevant material known to the public at that time will constitute the prior art in this case.[7] *See OddzOn Products, Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1402 (Fed. Cir. 1997) (citing *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1453 (Fed. Cir. 1984)).

A. Megestrol Acetate

At the time of the application for the '576 patent, Megace OS, a micronized oral suspension of megestrol acetate used in the treatment of anorexia, cachexia, and unexplained weight loss in HIV/AIDS patients, had been available on the market for almost ten years.[8] (Tr. 3:2 at 43:20-25.) It contained 40 milligrams (mg) of micronized megestrol acetate per milliliter (mL). (Megace OS Product Monograph, DTX 10 at ALK_M035677.) The recommended dosage was 800 mg/day (20 mL/day), but, according to the product monograph, doses of 400 and 800 mg/day were found to be clinically effective. (*Id.* at ALK_M035685.) Several prior art references disclose a once-daily dosage regime. (Graham et al., DTX 205 at 581; Oster et al, PTX 92 at 401; Camaggi et al., PTX 86 at 357.) In addition, it was known to be highly viscous, which could decrease patient compliance in taking the medication, as patients had to take a very large amount (20 mL) of the thick liquid. (DTX 1 at col. 6, ll. 49-51; Trial Tr. Day 1, Volume 2, [hereinafter Tr. 1:2], at 52:4-8; Trial Tr. Day 4, Volume 1, [hereinafter Tr. 4:1], at 83:8-15.) This was particularly problematic because the drug was used by patients who had trouble

[7] Although there may be certain instances in which non-public prior art known to the inventor may be considered in an obviousness analysis, *see OddzOn Products*, 122 F.3d at 1403-04, neither party appears to claim those circumstances are present in this case.

[8] Although Megace OS is only a particular embodiment of the prior art oral suspension of micronized megestrol acetate, for ease of discussion, the court refers to it as a proxy reference for the prior art.

swallowing. (Tr. 4:1 at 83:11-15.) Prior to the development of Megace OS, megestrol acetate had also been administered for a number of years as a tablet of 20 and 40 mg, in a dose of 160 mg/day or 40 to 320 mg/day in divided doses, and used for the treatment of advanced carcinoma of the breast or endometrium. (Tr. 3:2 at 43:12-19.)

At the time of the invention at issue in this case, in addition to the patent covering the name-brand Megace OS—U.S. Patent No. 5,338,732 ("Atzinger")—which issued in 1994, a patent had issued in 2000 covering Par's generic version of Megace OS—U.S. Patent No. 6,028,065 ("Ragunathan"), and a patent application was pending for another generic—Patent Application Pub. No. US 2002/0028704A1 ("Brubaker"). The Ragunathan inventors had altered the composition of the existing formulation and found "different formulations of flocculated megestrol acetate suspensions which are also stable." (PTX 97 at col. 2, ll. 57-59.) The Brubaker application was aimed at providing more "pharmaceutically elegant and stable" formulations of an oral suspension of micronized megestrol acetate. (DTX 332 at [0020], [0021].)

By 2002, researchers had made several discoveries concerning the efficacy of megestrol acetate. Several reported its success in increasing body mass in AIDS patients. (*See e.g.*, Graham et al., DTX 205 at 583, 584; Von Roenn et al., DTX at 238 at 398; Oster et al., PTX 92 at 406; Camaggi et al., PTX 86 at 356.) The Graham reference, published in 1994, studied the pharmacokinetics and absorption of the oral suspension formulation of micronized megestrol acetate and reported a statistically significant relationship between weight gain and the percentage of the 24-hour dosing period during which plasma concentrations exceeded 300 ng/mL. (DTX 205 at 581, 585.) Further, it found no significant relationship between total absorption and weight gain, suggesting that weight gain in the early stages of therapy required

exposure in vivo above a threshold concentration. (*Id.* at 585.) With respect to dosage, the authors noted, citing other studies as well, that the 800 mg dose "provides on average the most consistent degree of weight gain in both cancer and AIDS patients," but also suggested that dose individualization may be necessary given observed interpatient variability. (*Id.* at 583, 585.) Similarly, the Von Roenn reference, published in 1994 and studying the relationship between dosage and weight gain, disclosed that patients gained weight in a dose-dependent manner, with a statistically significant difference in weight gain between those receiving an 800 mg/day dose and a placebo. (DTX 238 at 394-96.) In addition to their own study, Graham et al. cited other studies disclosing weight gain in patients receiving doses of megestrol acetate between 160 and 1,600 mg/day, as well as studies disclosing variability in the response to the therapy, even in those receiving 800 mg/day. (DTX 205 at 584-85.) One study cited by the Graham reference reported that two of three patients who failed to gain weight at a 320 mg/day dose gained weight at higher doses (460-640 mg/day). (*Id.*)

Several studies published in 1994 also reported interpatient variability in response to the oral suspension of micronized megestrol acetate. The Graham reference reported "a high degree of interpatient variability" in pharmacokinetics—maximum plasma concentration ("C_{max}"), total absorption ("AUC"), and time to maximum concentration ("T_{max}")—with an eight-fold range in values in the rate of absorption and a five-fold range in values in the extent of absorption. (*Id.* at 582.) The authors also discovered two distinct patterns in absorption, with four of nine patients experiencing rapid absorption, with an initial elimination phase during the first 10 hours, and the other five experiencing more prolonged absorption followed by a slow decline. (*Id.* at 583.) The Von Roenn reference also reported interpatient variability in the effectiveness of Megace OS, noting that even within the group of patients receiving 800 mg/day, only about 64 percent

gained more than five pounds. (DTX 238 at 398.) Finally, Oster et al., studying the effects of Megace OS on weight gain, found that it did not stimulate weight gain in all patients. (PTX 92 at 406.) In addition, a study focused on bioavailability of solid dosage forms of micronized megestrol acetate found high interpatient variability in blood plasma levels and pharmacokinetic parameters. (Farinha et al., DTX 219 at 570 (noting that "megestrol acetate, with respect to C_{max}, behaves as a highly variable drug").) Although finding interpatient variability,[9] the prior art did nothing more than speculate as to the underlying causes. Graham et al. opined that variability in absorption may be due to factors altering gastrointestinal physiology, (DTX 205 at 584), while Oster et al. attributed variability in weight gain to the extent of wasting in the patient, (PTX 92 at 406).

TWi also claims that, in 2002, the prior art disclosed that Megace OS suffered from a food effect and poor bioavailability. While TWi has shown by clear and convincing evidence that it was known the steroid megestrol acetate was a BCS Class II drug and had poor bioavailability, (Tr. 2:2 at 92:11-15 (Dr. Beach's testimony); Farinha et al., DTX 219), the court does not find that TWi has demonstrated a known bioavailability problem with Megace OS.

By 2002, Farinha et al. had discovered that micronizing particles in a megestrol acetate formulation resulted in improved bioavailability. (DTX 219 at 569.) This demonstrates that one skilled in the art would have known megestrol acetate itself was not fully bioavailable. It does not, however, demonstrate whether a person skilled in the art would have known that micronizing the particles did not fully resolve the bioavailability issues, and TWi offers no other

[9] Par's expert Dr. Fleckenstein testified at trial that in the 2002-2003 timeframe, "there were really no reports of any problems of [Megace OS] in terms of efficacy or safety." (Tr. 3:2 at 62:10-11.) The court does not agree with this statement given the evidence from the Graham, Von Roenn, and Oster studies demonstrating interpatient variability. There clearly were reported efficacy problems in at least some patients.

evidence to demonstrate that Megace OS's specific bioavailability was known. TWi's claim that the Von Roenn study, (DTX 238), demonstrated a bioavailability problem is without merit. Finding that patients have a dose-dependent response to a drug does not provide evidence of bioavailability, without more. A drug could be fully bioavailable—meaning it is fully absorbed—but still be more effective at higher doses where more of the drug would be available for absorption.

Although not disclosing anything regarding the specific bioavailability of Megace OS, however, the prior art did disclose several things about Class II drugs, generally. First, it disclosed that Class II drugs had low solubility and high membrane permeability, and that slow dissolution rates were the primary limiting aspect to absorption. (Dressman & Reppas, DTX 281 at S73-74 (defining Class II drugs as those having "solubilities too low to be consistent with complete absorption").) Thus, it was known that, generally, bioavailability was a problem for Class II drugs. The inventors of nanoparticles stated as much during the prosecution of the U.S. Patent No. 5,145,684 ("the '684 patent"), the patent originally disclosing nanoparticles.[10] (DTX 5 at col. 1, ll. 17-20 ("Poor bioavailability is a significant problem encountered in the development of pharmaceutical compositions, particularly those containing an active ingredient that is poorly soluble in water."); *see also* DTX 6B at 5 (stating the same in a filing in the prosecution of the '684 patent).) The prior art also disclosed that "[a]ny interaction that increases solubility and dissolution rate in the gastrointestinal ("GI") tract will have a positive effect on GI absorption of class II drugs," and listed taking drugs with meals as one means of doing so. (DTX 316 at 245.) The prior art also disclosed, however, that many factors can affect dissolution rates in a drug—both physical and physiological—and that absorption will not be the

[10] Elan's touting of nanotechnology's benefits for poorly soluble drugs also provides evidence of this. (DTX 13 at PAR-MEG945718; DTX 177 at 1.)

same across all drugs in the same class or in all individuals. (*See* DTX 281 at S74; DTX 316 at 237, 238 tbl. III & IV; *see also* FDA Guidance for Industry, PTX 83 at 2.) The Dressman & Repas reference disclosed that particle size "is an important physical determinant of the surface area available for dissolution." (DTX 281 at S74.)

The remaining evidence to which TWi points regarding food effects and bioavailability does not convincingly demonstrate that, by April 2002, one skilled in the art would have known the extent of Megace OS's bioavailability, or that Megace OS, or megestrol acetate for that matter, was more effectively absorbed when taken with food. First, TWi points to what was known about danazol, another poorly soluble steroid classified as a BCS Class II, and expressly listed in the prior art as having poor bioavailability and a food effect. (DTX 5 at Example 2 (noting improved bioavailability in danazol when formulated with nanoparticulates); DTX 316 at 245-46, 246 tbls. IX & X (noting danazol's improved absorption when taken with a high-fat meal).) TWi claims a person skilled in the art would have known in 2002 that megestrol acetate was similar to danazol such that it would behave like danazol with respect to food effects. The only evidence TWi proffered, however, is Dr. Beach's testimony at trial that he believed danazol and megestrol acetate were similar because they share a four-ring structure, as all steroids do, (Tr. 2:2 at 72:20-23:5), and a statement by a Par representative in a 2001 email noting that those testing the nanoparticulate formulation of megestrol acetate expected a reduction in fed-fasted variability based on the data they had for danazol, "which is almost structurally identical." (DTX 120.) The statement made by Par cannot provide any guidance on what was known in the prior art; the statement was not publicly available and there is no indication of the basis for the statement. Further, Dr. Beach's testimony cannot be credited given Dr. Fleckenstein's testimony that a person skilled in the art would have known the two steroids had different

absorption mechanisms and, although sharing the four-ring structure of all steroids, had other structural differences that affected absorption. (Tr. 4:1 at 76:2-77:19, 78:16-79:25.) TWi offers no evidence addressing his testimony. The court thus finds that TWi has not offered clear and convincing evidence that danazol's similarities to megestrol acetate were enough for a person skilled in the art to conclude that megestrol acetate would suffer from the same food effect or have the same absorption rates as danazol.

Second, TWi points to statements made by Par, Alkermes—then known as Elan—their representatives, and the FDA that patients were instructed to take Megace OS with food. All the statements, however, were made well after April 2002, and TWi provides no evidence that the statements reflect what was known in April 2002. Dr. Liversidge's statement that "you had to take [Megace OS] with food," is from his testimony in a 2008 trial. (*See* Tr. 1:2 at 50:18-51:11, 52:3-16.) There is nothing in Dr. Liversidge's testimony to indicate when the food effect was discovered; there is nothing to suggest it was not discovered at the time a nanoparticulate formulation was first made, as Par claims.

The statements made by the FDA and Par while Par was seeking a New Drug Application ("NDA") for Megace ES were not separate statements at all. Instead, the initial statement that "patients are instructed to take Megace OS with food," was made by an FDA representative in a letter dated September 10, 2003, well over a year after the critical date for determining the prior art, and all subsequent statements TWi points to were actually references to that original letter. (*See* DTX 83 at PAR-MEG281946 (FDA's September 10, 2003 letter to Par stating, "patients are instructed to take Megace with food"); DTX 86 at PAR-MEG94451 (Par's response to the FDA's September letter repeating the FDA's prior statement); DTX 255 at PAR-MEG322900 (relaying the FDA's statement to clinical trial site directors in 2004); PTX

3A at PAR-MEG000370 (Par's NDA repeating the statement from the FDA's letter and attributing it to that letter); DTX 546 at ALK_M121566 (same).) As with Dr. Liversidge's 2008 testimony, TWi provides no evidence that the statement made by the FDA reflected knowledge in April 2002 or was not a result of what Par claimed to have discovered about Megace OS when developing the nanoparticulate formulation.

TWi also points to Elan's website and various drafts of it that appear to be from, at the earliest, 2006, stating that the oral suspension of micronized megestrol acetate had to be taken with food. (DTX 116 at ALK-M160963; DTX 183 at 1; DTX 184 at ALK_M019448.) Again, TWi provides no evidence that the statement reflects knowledge in 2002 and is not the result of hindsight.

Third, TWi relies on the Graham reference as proof that Megace OS was known to be more effective when taken with food. Its claim is based entirely on the fact that the Graham authors instructed patients to take their daily dose of the oral suspension before breakfast and then, when testing plasma concentrations, had the patients take their dose after an overnight fast with a low-fat breakfast following two hours later. (DTX 205 at 581.) The court finds no support for TWi's claim that the Graham reference demonstrates that those skilled in the art knew absorption of Megace OS was enhanced when taken with food. TWi's apparent claim that the authors were trying to minimize the known food effect by having patients take their doses in a fasted state is unpersuasive in light of Dr. Fleckenstein's testimony that investigators administering a drug study to human patients would want to ensure they were administering the drug in optimal conditions, to make it as effective as possible. (Tr. 3:2 at 79:14-25.) If the Graham investigators knew the drug was more effective when taken with food as TWi alleges, it does not make sense that they would purposefully make it less effective by having patients take it

in a fasted state. The Graham reference does not demonstrate a known food effect in the absorption of the oral suspension of micronized megestrol acetate.

Finally, TWi relies on the '576 patent inventors' statement in the patent's specification that "[t]here is a need in the art for megestrol formulations which exhibit increased bioavailability." (DTX 1 at col. 4, ll. 28-29.) It is true that statements of the prior art in a patent's specification are binding on the patentee when determining obviousness. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007). The '576 inventors' statement is not, however, best characterized as a statement of what was in the prior art in 2002. In the cases on which TWi relies to convince this court otherwise, the inventors expressly identified references as "prior art" or expressly stated what was previously known from the prior art. *See, e.g., id.* at 1361-62; *Constant v. Adv. Micro-Devices, Inc.*, 848 F.2d 1560, 1569-70 (Fed. Cir. 1988); *In re Nomiya*, 509 F.2d 566, 570-71 (C.C.P.A. 1975). By contrast, there is nothing to suggest the statement in the '576 patent specification is anything more than the inventors' own evaluation of the prior art upon inventing the nanoparticulate formulation of megestrol acetate, nor do there appear to be prior art references cited in the specification from which the statement about bioavailability is drawn. Eurand's "modified form of megestrol acetate having increased bioavailability," cited in the specification, is not clearly prior art as there is no indication of when it would have been known to a person skilled in the art.[11] (DTX 1 at col. 4, ll. 4-20; *see also* Tr. 4:1 at 100:6-13 (Dr. Fleckenstein's testimony that it was true that Eurand "advertised they also were trying to develop a megestrol product with improved increased bioavailability").) Further, there is no indication of whether Eurand's formulation is a

[11] In fact, the only evidence TWi provides of when the Eurand formulation was disclosed is an email calling the work to the attention of several individuals associated with Par and dated October 30, 2002. (DTX 130 at ALK_M002623.) The webpage included with the email has a copyright year of 2002, with no specific date listed. (*Id.* at ALK_M002624.)

modification of conventional or micronized megestrol acetate. As discussed earlier, it was known conventional forms of megestrol acetate suffered from bioavailability problems. For these reasons, although the Eurand invention may suggest others were aware of a bioavailability problem, the '576 inventors citation to it is not an admission of prior art that provides clear and convincing evidence of what was known about micronized megestrol acetate formulations.

That TWi has failed to prove a known food effect is further bolstered by the fact that Graham and other researchers, in several studies conducted in 1994, 1995, and 2000, instructed participants to take Megace OS without food. (*See* Graham et al., DTX 205 at 581; Oster et al., PTX 92 at 401; Camaggi et al., PTX 86 at 357; Farinha et al., DTX 219 at 568.) In addition, Dr. Wanke, a doctor and academic focusing on infectious diseases—predominantly HIV and AIDS—and nutrition and metabolism issues associated with such diseases, testified that during the 1990s, while an attending physician at a Harvard-affiliated hospital, she did not tell hundreds of HIV/AIDS patients for whom she prescribed Megace OS to take it with food, because neither she nor others at the clinic knew of the food effect. (Tr. 4:2 at 20:17-21:9.) Further, the product monograph for Megace OS expressly reported, in 2002, that "the effect of food on the bioavailability of Megace [OS] has not been evaluated."[12] (DTX 10 at ALK_M035679.) The product monograph, Dr. Wanke's testimony, the manner in which the prior art studies were conducted, and Dr. Fleckenstein's testimony that those conducting human trials would attempt to administer the drug in the most effective manner (Tr. 3:2 at 79:3-25), provide substantial

[12] TWi claims this statement cannot be credited because the label as of 2012 still said the food effect had not been studied even though Par's study results were well known in 2012. Although the statement may not be a proper reflection of the art as it exists today, however, TWi has failed to offer any reason to believe it did not reflect what was known in the prior art in 2002.

evidence that the food effect was unknown.[13]

B. Nanoparticulate Technology

The prior art includes several patents disclosing the attributes and advantages of nanoparticles. The '684 patent first disclosed nanoparticles in 1992. (DTX 5.) It disclosed particles with an effective average size of less than about 400 nanometers (nm), 250 nm, or 100 nm. (*Id.* at Claims 1-3, 6, 9-10, 16, 17.) It also disclosed the use of a surface modifier with the chosen drug substance, and stated that it was "believed that the surface modifier hinders the flocculation and/or agglomeration of the particles by functioning as a mechanical or steric barrier between the particles, minimizing the close, interparticle approach necessary for agglomeration and flocculation." (*Id.* at col. 4, ll. 28-30, col. 8, ll. 21-27.)

The patent specification disclosed that the invention could be practiced with a number of drug substances, preferably those intended for oral and intravenous administration, as long as they were poorly soluble. (*Id.* at col. 3, l. 32-col. 4, l. 20.) In fact, the inventors stated during the patent's prosecution that the "invention can be practiced with *virtually all* poorly soluble drug substances," provided numerous examples of successfully-made nanoparticles, and stated that the examples "illustrate[d] that eleven soluble drug substances of radically different chemical structure and from a wide variety of therapeutic classes have been prepared in the form of

[13] Par points to two other references—Schindler et al. (2003), (PTX 117), and the FDA's approval of Roxane Laboratories' ("Roxane") generic version of Megace OS (PTX 513)—which it claims undercut any finding that Megace OS was known to have poor bioavailability or suffer from a food effect, (Pl.'s Brief at 11), but the court does not find them persuasive. First, there is no evidence that either constitutes a prior art reference: Schindler was published in 2003 and, although the approval date of Roxane's generic was February 15, 2002, there is no evidence of when its contents were made public. Second, the Schindler reference offers no evidence or reasoning to support its claim that "the bioavailabilty of [megestrol acetate] is nearly 100%," (PTX 117 at S12), and in the face of Farinha et al., (DTX 219), it carries little weight with the court. The FDA file on Roxane's generic only states that megestrol acetate is "well absorbed," with no indication of how "well absorbed" is empirically defined (PTX 513 at PAR-MEG573872.).

nanoparticles." (DTX 6B at 8 (emphasis added).) The '684 patent specifically listed "sex hormones (including steroids)" as a preferred drug substance, with danazol and steroid A providing representative examples, sharing several nanoparticulate formulations of the two drugs. (DTX 5 at col. 4, l. 3, col. 4, ll. 15-20, col. 8, l. 36-col. 15, l. 26, Claim 5; *see also* DTX 6C at ¶ 7 (statement by the '684 patent inventors that "[l]aboratory work has demonstrated that the wet grinding process . . . is broadly applicable to a wide variety of classes of poorly-soluble drug substances including steroids").)

In addition, the '684 patent specification stated that "pharmaceutical compositions according to this invention include the particles described above and a pharmaceutically acceptable carrier therefor . . . includ[ing] . . . acceptable carriers . . . for oral administration," and that "[i]t is contemplated that the pharmaceutical compositions of this invention will be particularly useful in oral . . . administration." (*Id.* at col. 7, ll. 53-60, col. 8, ll.10-13.) Finally, the patent disclosed that the invention related to the use of nanoparticles in pharmaceutical compositions and methods of treating mammals. (*Id.* at col. 1, ll. 8-10, col. 2, ll. 57-62; *see also id.* at col. 7, ll. 60-64 ("A method of treating a mammal in accordance with this invention comprises the step of administering to the mammal in need of treatment an effective amount of the above-described pharmaceutical composition."), Claim 15.)

United States Patent No. 5,399,363 ("the '363 patent"), entitled "Surface Modified Anticancer Nanoparticulates" and issued in March 1995, and European Patent No. 0577215B1 ("the '215 patent"), entitled "Process for Obtaining Surface Modified Anticancer Nanoparticles" and issued in March 2000, followed the '684 patent and claimed nanoparticulate formulations of anticancer agents that exhibit reduced toxicity and/or enhanced efficacy.[14] (DTX 3 at [45], [57];

[14] The '215 patent is essentially the European version of the '363 patent.

DTX 11 at (45), [0005].) Both patents disclose that the claimed invention can be practiced with a wide variety of anticancer agents as long as they are poorly soluble, and both expressly list megestrol acetate as one of many preferred anticancer agents.[15] (DTX 3 at col. 2, ll.35-38, ll.50-53, col. 3, ll.22-26; DTX 11 at [0015], Claim 1.) Further, both patents disclose that the claimed compositions could include an acceptable carrier for oral administration. (DTX 3 at col. 7, ll. 53-61, col. 8, ll. 53-58; DTX 11 at [0038].) In addition, both claim an effective particle size of less than 1000 nm and 400 nm, respectively, and disclose the use of a surface modifier absorbed on the surface of the anticancer agent sufficient to maintain the particle size and ensure the dispersion "exhibits no particle flocculation or particle agglomeration visible to the naked eye and particularly when viewed under the optical microscope at 1000x at least two days after preparation." (DTX 3 at Claim 1; DTX 11 at [0006], Claim 1.) Like the '684 patent, the '363 and '215 patents also claim a method of treating mammals by administering an effective amount of the resulting composition, and further claim increased efficacy and reduced toxicity. (DTX 3 at Claims 9-11; DTX 11 at [0010], [0039].)

Several prior art references disclosed the potential benefits of nanoparticulate technology. In the prosecution of the '684 patent, the inventors disclosed that nanoparticulate formulations of two steroids, Steroid A and danazol, demonstrated seven and sixteen fold increases, respectively, in bioavailability over conventional formulations when tested in dogs. (DTX 6C at ¶ 8; DTX 5

[15] Citing cases examining whether a prior art reference anticipated the challenged claims, Par attempts to argue the '363 and '215 patents did not disclose that megestrol acetate was a suitable agent to be used with nanotechnology because it was just one of many on a list of suitable agents and there is nothing directing a person skilled in the art to choose megestrol over others. That a compound may be one of many on a list, however, does not undermine the disclosure. *See In re Gleave*, 560 F.3d 1331, 1337-38 (Fed. Cir. 2009); *Perricone v. Medicis Pharm. Co.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005). Because this is a case under § 103, it does not matter whether the '215 and '363 patents enabled the claimed formulation of the '576 patent, only that they disclosed that megestrol would be a suitable agent to be used in such formulations.

at col. 9, l. 60-col. 10, l. 11). Observing the increased bioavailability of a nanoparticulate suspension of danazol in dogs over the conventional formulation, the '684 patent inventors therefore reported that the results "suggest[ed] that the nanoparticulate dispersion had overcome the dissolution rate limited bioavailability" of conventional suspensions of danazol. (DTX 15 at 97.) The '684 patent inventors also stated in filings with the U.S. Patent Office that particles prepared with the nanotechnology could be formulated into "pharmaceutical compositions exhibiting remarkably high bioavailability and other advantageous properties, including, for example, improved dose proportionality, decreased fed-fasted variability and more rapid onset of action." (DTX 6B at 7; *see also* DTX 6C at ¶ 9 ("Pharmaceutical compositions containing particles prepared according to the method . . . have exhibited improved dose proportionality and decreased fed-fasted variability.").) By 2001 and early 2002, Elan's website and brochure on its NanoCrystal technology (nanoparticulate technology) publicly touted the potential to increase bioavailability, reduce fed-fasted effects, allow higher dose loading with smaller dose volume, decrease time to therapeutic levels, and reduce viscosity in poorly soluble drugs.[16] (DTX 177 at 2; DTX 13 at PAR-MEG945718-19; *see also* Müller et al. (2000), DTX 16 at 401, 403 (noting nanoparticles resulted in increased bioavailability, increased dose proportionality, reduced fed-fasted effects, reduced intersubject variability, and enhanced absorption rates).) The Müller reference, from 2000, disclosed that nanoparticles reduced erratic absorption—interpatient variability—because the adhesion process associated with nanoparticles was highly reproducible

[16] TWi also introduced slides from a presentation allegedly given in Kyoto in 1996 on the benefits of nanoparticles. (DTX 314.) The court will not rely on the exhibit as prior art, however, because TWi has failed to show by clear and convincing evidence that it was in fact the presentation given in 1996, (*see, e.g.*, Tr. 1:2 at 29:8-15), and thus has failed to show that the slides would have been those publicly available, *see Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1305 (Fed. Cir. 2006) ("Art that is not accessible to the public is generally not recognized as prior art.").

and little affected by the nutritional status of the patient. (DTX 16 at 403.)

In addition, and more generally, it was known in the prior art that reducing particle size, either to nanoparticlulate or microparticulate size, could increase the bioavailability of poorly soluble drugs. (*See* Müller et al., DTX 16 at 384-85 (discussing the need to further reduce particles to nanoparticulate size in the most poorly soluble drugs to increase bioavailability by increasing the dissolution rate); U.S. Patent 6,045,829, DTX 188 at col. 1, ll.36-52 (discussing the problem of poor bioavailability due to poor absorption in poorly soluble drugs and stating "it is known that by increasing the surface area of a particulate drug, such as by decreasing the particle size of the drug, the rate of dissolution of the particulate drug is increased"); U.S. Patent 6,221,400, DTX 182 at (57) (same).) One study specifically found that a 160 mg dose of micronized megestrol acetate exhibited higher bioavailability than a 160 mg dose of non-micronized megestrol acetate. (Farinha et al. (2000), DTX 219 at 569.) Further, the Müller reference disclosed the superiority of reducing particle size to address issues of solubility over other possible solutions, and found that, when higher blood levels are required, micronizing particles was not enough of a reduction in size. (DTX 16 at 384.)

V. Differences between the Prior Art and the Claimed Invention and Prima Facie Obviousness

TWi has proved by clear and convincing evidence a prima facie case of obviousness. Not only does the prior art disclose every element of the challenged claims, but it discloses a motivation for a person of ordinary skill in the art to combine the elements in the way disclosed by the '576 patent and to do so with a reasonable likelihood of success. *See In re Cyclobenzaprine*, 676 F.3d at 1068-69 ("Generally, a party seeking to invalidate a patent as obvious must demonstrate . . . that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan

would have had a reasonable expectation of success from doing so."); *Broadcom*, 732 F.3d at 1335 (noting that "[a]n invention is not obvious just 'because all of the elements that comprise the invention were known in the prior art.").

A. The prior art discloses all elements of the claimed invention.

As discussed in Part IV, the prior art disclosed the use of an oral suspension of megestrol acetate for increasing body mass in HIV/AIDS patients suffering from anorexia, cachexia, or unexplained weight loss—this is Megace OS and its generic replications. Further, the prior art disclosed the claimed single daily administration and dose range (claims 1, 4), as Megace OS had been administered daily and in doses within the range of 40 mg to 800 mg. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (finding a claimed range obvious where it overlapped with that disclosed in a prior art reference); *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (same). Further, the doses claimed do not represent optimization and there is no evidence they achieve unexpected results on their own. *In re Geisler*, 116 F.3d at 1469. The prior art disclosed each of the claimed therapeutic blood levels as well: a mean T_{max} of five hours, (Graham et al, DTX 205 at 582, tbl. 2), a therapeutically effective threshold blood level of 300 ng/mL, (*id.* at 585), steady-state C_{max} levels ranging from 295 ng/mL to 1,670 ng/mL, (*id.* at 582, tbl. 2), and increased C_{max} levels in formulations with reduced particle sizes (Farinha et al., DTX 219 at 570). The prior art also disclosed nanoparticulates, their use in pharmaceutical compositions for oral administration,[17] and how to create stable formulations using surface modifiers. In addition, the '215 and '363 patents expressly disclosed nanoparticle formulations

[17] Par claims that the '363 and '215 patents do not disclose oral administrations of nanoparticulate megestrol acetate because the patents are focused on intravenous ("IV") administrations. This argument is without merit. Whatever the primary purpose of the prior art, a person skilled in the art may find a teaching in addition to that purpose. *KSR Int'l Co.*, 550 U.S. at 421.

using megestrol acetate as the drug substance.

Par claims that the prior art does not disclose the claimed differences, or lack of substantial difference, between the C_{max} of megestrol in a fed versus fasted state (Claims 1, 4, 5). The claimed pharmacokinetic parameters with respect to a food effect, however, are inherent properties of the obvious nanoparticulate formulation claimed by the '576 patent, and, although functional limitations, they do not render the obvious formulation and method nonobvious.

Inherency may be considered in an obviousness analysis. *See Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2013); *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011), *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009). A property that inherently results from an obvious combination of the prior art, although previously unknown, does not render the combination nonobvious. *See Allergan Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1294 n.1 (Fed. Cir. 2013) (suggesting that where the evidence establishes a claimed limitation is the necessary result or inherent property of a claimed administration it does not render an otherwise obvious claim nonobvious); *In re Kao*, 639 F.3d at 1070 (finding an inherent property of a compound used in a claimed method did not render the obvious claimed method nonobvious even though the property was unknown in the prior art); *cf. In re Best*, 562 F.2d 1252, 1254-55 (C.C.P.A. 1977) ("[W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on." (citation omitted)).

As discussed below, TWi has proven by clear and convincing evidence that combining nanotechnology with megestrol acetate would have been obvious to someone skilled in the art

because of the viscosity and interpatient variability associated with the micronized formulation. As Dr. Beach testified, an improvement in bioavailability necessarily results in a reduction in any food effect, whether previously known or not. (Tr. 3:1 at 11:11-12:5.) TWi has demonstrated that reducing particle size will improve bioavailability across all administrations claimed in the invention, thus any food effect will inherently be reduced. It is, therefore, an inherent result or property of the administration even if it was previously not known in the prior art that a food effect existed. "To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Santarus*, 694 F.3d at 1354.

Par's attempt to liken this case to *In re Newell* is unconvincing. In that case, the Federal Circuit found the inventor had no motivation to combine the prior art other than his discovery of a previously unknown problem. 891 F.2d 899, 901-02 (Fed. Cir. 1989). Accordingly, the court found it was improper for the Board of Patent Appeals to rely on the inherency of the problem, and the inherency of the improvement, to find the invention obvious. *Id.*; *see also Leo Pharm. Products, Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013). Here, the court is not using inherency as a hindsight substitute for motivation. Instead, the court has found motivations other than the food effect for combining the prior art, and the inherent property of a reduced food effect does not negate that.[18] *See In re Kao*, 639 F.3d at 1070 ("This is not a case where the

[18] It does not appear that any possible food effect associated with Megace OS was what motivated Par to create the nanoparticulate formulation in the first place. (*See* DTX 129 (noting the dog study disclosing the food effect was performed after Elan's Dr. Pruitt created the formulation); DTX 199 at 1, 4 (discussing the parameters of the dog study after the first successful formulations had been created); DTX 353 at 97:12-98:09 (Dr. William Bosch's deposition testimony that the dog trials were performed "to determine whether or not the reformulation had an impact on pharmacokinetics of the product").) Indeed, the evidence does not provide much insight into why Par pursued the nanoparticulate formulation of megestrol acetate. Dr. John Pruitt, one of the '576 inventors, testified at his deposition that, ordinarily, he

Board relied on an unknown property of prior art for a *teaching*. Rather, [the prior art's] express teachings render the claimed [formulation] obvious, and the claimed 'food effect' adds nothing of patentable consequence.").

B. The prior art provided a motivation for a person skilled in the art to combine the prior art elements.

Given that all the elements are disclosed in the prior art, the essential inquiry for determining obviousness in this case is whether a person of ordinary skill in the art would have seen a benefit to applying the nanoparticulate technology disclosed in the prior art to Megace OS and been motivated to do so. "[M]otivation to combine may be found explicitly or implicitly in market forces; design incentives; the interrelated teachings of multiple patents; any need or problem known in the field of endeavor at the time of invention and addressed by the patent; and the background knowledge, creativity, and common sense of the person of ordinary skill." *Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1354 (Fed. Cir. 2013) (internal citations and quotation marks omitted). The prior art does not have to expressly teach the invention at issue. It is enough if the prior art would have suggested the invention to a person skilled in the art. *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

Although the court finds TWi has failed to prove by clear and convincing evidence that one skilled in the art would have known of the food effect associated with Megace OS and the extent of its bioavailability problem, there were other motivations to improve the existing formulation. *See KSR Int'l Co.*, 550 U.S. at 420 ("[T]he problem motivating the patentee may be only one of many addressed by the patent's subject matter. The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person

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was just told to see if he could create a stable formulation, while Dr. Bosch stated in an email at the beginning of the project that Par was seeking to make a more bioavailable formulation. (DTX 119; DTX 352 at 15:7-12.)

with ordinary skill in the art."); *Alcon*, 687 F.3d at 1368 ("We have repeatedly held that the motivation to modify a prior art reference to arrive at the claimed invention need not be the same problem the patentee was trying to solve."). TWi proved it was known that Megace OS was viscous and required more dosing and that absorption levels varied greatly among patients. The court finds that both of these problems provided sufficient motivation for a person skilled in the art to create a method of treatment using nanoparticles.

Dr. Fleckenstein testified that Megace OS was known to be highly viscous and that this created difficulties in the patient population because AIDS patients have difficulty swallowing viscous materials. (Tr. 4:1 at 83:8-15; *see also* Tr. 1:2 at 52:4-6 (Dr. Liversidge's testimony that the formulation was very viscous).) When asked by the court, he also testified that switching to the nanoparticulate formulation would be expected to help with the viscosity problem. (*Id.* at 16-23.) In addition, Dr. Liversidge testified that Megace OS was administered in a half-cup dose. (Tr. 1:2 at 52:6-8.) Par attempts to minimize the motivation that viscosity and large dose volume would provide by claiming they were merely a cosmetic factor of secondary concern to physicians. (Pl.'s Reply, ECF No. 205, at 14-15 (citing Tr. 4:1 at 84:10-12; DTX 24 at 4).) This flies in the face, however, of Dr. Fleckenstein's testimony and the acknowledgment in the '576 patent specification that "[t]ypical commercial formulations of megestrol, such as Megace, are relatively large volume, highly viscous substances that are not well accepted by patient populations, particularly subjects suffering from wasting." (DTX 1 at col. 6, ll. 49-51.) In addition, Par's marketing consistently emphasized reduced volume and reduced viscosity as benefits of Megace ES, seemingly reflecting a known, existing desire among those prescribing Megace OS for a less viscous, lower volume formulation. (*See, e.g.*, PTX 241 at PAR-MEG150891 (training materials for new hires stating that less volume and reduced viscosity "is

an important point with physicians who are treating patients with decreased or no appetite, and may have difficulty swallowing"); PTX 249 at PAR-MEG382865 (listing reduced volume and viscosity as "patient benefits"); PTX 449 at PAR-MEG100199 (including reduced volume and viscosity on marketing materials as features demonstrating "there's more to gain with Megace ES"; *see also* Tr. 5:1 at 83:9-18 (Dr. Vandaele's testimony that reduced volume and viscosity were part of "the three main messages" in marketing Megace ES).) In fact, in its post-trial brief, Par stated that "reduced volume" and "reduced viscosity" were "core messages" of its marketing materials. (Pl.'s Brief at 40-41.)

Par points out that others reformulating oral suspensions of megestrol acetate did not use nanotechnology to change viscosity. Yet, Par relies on the patent covering Megace OS—Atzinger—and a patent application for a generic form of Megace OS—Brubaker—to make this claim. The question at issue in this case is whether there was a motivation to change the existing oral suspension of *micronized* megestrol acetate, not conventional formulations. Further, it is unlikely that an inventor focused on creating a generic formulation of an already marketed drug would change an underlying structural aspect of the compound—such as particle size—where he must show bioequivalency to the FDA.

In addition to high viscosity and dose volume, the prior art taught that the oral suspension of micronized megestrol acetate suffered from high interpatient variability in drug absorption and weight gain, (DTX 205 at 582-83; DTX 238 at 398; PTX 92 at 406), providing another motivation to use nanoparticles to reformulate the drug. Although one skilled in the art would not have known the specific extent of the bioavailability problems of Megace OS, the person would have been aware that the underlying compound of megestrol acetate was poorly soluble and not fully bioavailable as demonstrated by the increase in bioavailability when it was

reformulated from the conventional particle size to micronized particles. (Farinha, DTX 219.) Further, the person would have known that it was a Class II drug and that absorption of such drugs are dissolution-rate limited such that "[a]ny interaction that increases solubility and dissolution rate in the GI tract will have a positive effect on GI absorption of class II drugs." (DTX 316 at 245.) A person skilled in the art also would have been aware that reducing particle size affects dissolution rates and that the smaller the particle size, the more surface area available for absorption, thus increasing dissolution velocity. (DTX 16 at 384.) This, along with the fact that reducing particle size had improved the bioavailability of megestrol acetate before, would have suggested to a person skilled in the art that the remaining variability in absorption levels in some patients may be due to bioavailability problems and that nanotechnology could address those issues in some patients. (*See* Tr. 3:1 at 9:17-11:13.) Although it does not constitute a prior art reference, Dr. William Bosch, at Elan, seems to have recognized the desire to improve bioavailability when he noted at the beginning of the project to reformulate Megace OS that "Par would like to see about developing a more bioavailable form of the liquid product." (DTX 119.) Nanotechnology would have been especially appealing given the Oster and Graham references that attributed interpatient variability to a patient's wasting or changes in their gastrointestinal physiology, (DTX 205 at 584; PTX 92 at 406), because the prior art disclosed that nanoparticulates' adhesion process was little affected by the nutritional status of the patient, (DTX 16 at 403). Given that using nanoparticles had the added benefit of reducing viscosity and dose volume, a person skilled in the art thus would have been motivated to use the technology to improve upon all known problems with one solution.

Dr. Fleckenstein disputed that interpatient variability would have provided a motivation to create a nanoparticulate formulation of megestrol acetate, testifying that the 64% success rate

reported in the Von Roenn study was "remarkable" given that weight loss in AIDS patients is very complicated and results from a number of causes. He thus concluded that Megace OS was "remarkably effective" and would leave those skilled in the art with no motivation to improve upon it with nanotechnology. (Tr. 3:2 at 67:3-18.) The court finds it unlikely that those skilled in the art would not be interested in determining why Megace OS was only effective in a little over half of patients or in finding a way to make it more effective. The court further finds Dr. Fleckenstein's testimony to be less persuasive because it is also based on the Schindler reference, (Tr. 3:2 at 67:19-68:9), which as discussed above conclusively states that megestrol acetate is nearly 100 percent bioavailable with no underlying evidence or reasoning, *see supra* note 13.

The application of nanotechnology to megestrol acetate would not have been just "obvious to try," such that it constituted throwing "metaphorical darts at a board filled with combinatorial prior art possibilities." *In re Kubin*, 561 F.3d at 1359. The Federal Circuit has identified two classes of cases in which "obvious to try" is erroneously equated with obviousness under § 103. In the first, a patent is not invalid for obviousness where the prior art only made it obvious to try varying all parameters or to try each of numerous possible choices with no indication of which were critical parameters or which choices would lead to a successful result. *Id.* In the second, a claimed invention is not obvious under § 103 where it was only obvious to explore a new technology or general approach that seemed to be a "promising field of experimentation," but offered nothing more than "general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* (internal citation and quotation marks omitted). Neither of those scenarios is present in this case. TWi has proven that the problems known to exist with Megace OS were its viscosity, dose volume, and its varied efficacy in patients, and that each were known to be affected by a drug's particle size. It was not a matter of trying to

change various parameters or trying different solutions hoping one would solve the problem. The benefits of reducing particle size were known with respect to all known problems. Further, even if Par's expert, Dr. Berkland, is correct that there were other ways to address these issues that were less complex and tested, the list he provides is finite, (Tr. 5:1 at 14:1-15:23), and "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp." *KSR Int'l Co.*, 550 U.S. at 421. Although nanotechnology may have been relatively new and untested, the nanotechnology patents provided a clear method for creating stable nanoparticles. The prior art did not merely direct those skilled in the art to reduce particle size, by whatever means a person could find. It provided a clear path forward with a clear prediction of the result.

C. The prior art did not "teach away" from the claimed invention.

Par claims that the Graham reference and known agglomeration of nanoparticles taught away from the claimed invention. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Kubin*, 561 F.3d at 1357 (internal citations and quotation marks omitted). According to Par, Graham's study of the pharmacokinetic and pharmacodynamic properties of Megace OS taught that more rapid absorption would lead to poorer patient outcomes and no weight gain and thus discouraged the use of nanotechnology which was known to lead to more rapid absorption. (Pl.'s Reply at 11.) Par bases its claim on Graham's finding that study participants experiencing more prolonged absorption and slower elimination also experienced superior weight gain. (DTX 205 at 584-85.) Par distorts the teaching of Graham, however.

From the difference in outcomes, Graham found a statistically significant relationship between weight gain and the percentage of the 24-hour dosing period during which plasma concentrations exceeded 300 ng/mL when patients were administered Megace OS. (*Id.* at 585.) From this Graham et al. concluded that "weight gain in the early stages of megestrol therapy requires drug exposure in vivo above a threshold concentration" and that weight gain would likely occur "when plasma megestrol concentrations exceed 300 ng/mL for at least 40% (10 h) of a 24-h dosing interval." (*Id.*) A person skilled in the art thus would have concluded that the longer a patient's blood plasma concentration could be maintained above the 300 ng/mL threshold, the better. To properly teach away from a claimed combination, the prior art reference must "criticize, discredit, or otherwise discourage the solution claimed." *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Although cautioning a person skilled in the art that rapid absorption with rapid elimination and low blood plasma concentrations may cause Megace OS to be ineffective, Graham did not discredit a nanoparticulate formulation or teach that it would not have worked for its intended treatment purposes. *See id.*; *In re Icon Health*, 496 F.3d 1374, 1381 (Fed. Cir. 2007) ("[A] reference may teach away from a use when that use would render the result inoperable."). Nanoparticles were known to increase absorption levels and were associated with longer dose retention, (*See* DTX 177 at 2), features that ostensibly would contribute to higher concentration levels for longer time periods. The Graham reference nowhere suggests that rapid absorption when combined with these features would prevent sustained blood plasma levels above the effective threshold or that the resulting formulation would be wholly ineffective in sustaining blood concentrations for an effective time period, and thus cannot be said to discourage investigation into the claimed invention.

Par also claims that agglomeration was a known problem with nanoparticles and would

have taught away from combining the prior art in the way claimed by the '576 patent. (Tr. 5:1 at 16:10-17:8.) This argument is without merit as well. Although smaller particles may have resulted in a greater risk of agglomeration, the nanotechnology patents demonstrated that use of a surface modifier with nanoparticles could prevent agglomeration. (*See, e.g.*, DTX 5 at col. 8, ll. 21-27; DTX 11 at Claim 1.)

D. A person skilled in the art would have had a reasonable likelihood of success in creating the claimed invention.

Despite the touted benefits of nanotechnology for poorly soluble compounds, Par claims TWi has failed to demonstrate a person skilled in the art would have had a reasonable likelihood of success because nanotechnology was new, untested, and unpredictable. TWi has demonstrated by clear and convincing evidence, however, that a person skilled in the art in 2002 would have believed making nanoparticles was not extremely difficult, could successfully be implemented with a wide variety of drugs, particularly steroids, and would result in reduced interpatient variability, improved bioavailability, reduced viscosity and reduced dosing volumes. As discussed above, the expected benefits of nanoparticles were widely touted by 2002. Further, the relevant prior art references described the wide applicability of nanotechnology for creating pharmaceutical compositions and its "simplicity," with several examples of success. (*See* DTX 3 at col. 7, l. 51-col. 8, l. 5; DTX 5 at col. 3, l. 32-col. 4, l. 20; DTX 6B at 8; Müller et al., DTX 16 at 406 ("[T]he major advantage of this technology is its simplicity.")

Par claims Dr. Liversidge's, one of the '684 inventors, testimony at trial, that it is hard to predict which compounds can be successfully formulated with nanoparticles and that success is varied even among poorly soluble drugs, undermines this conclusion. (*See* Tr. 1:2 at 70:6-74:13.) Par further points to the fact that, as of trial, only six commercialized formulations with nanoparticles had made it to market. (*Id.* at 69:9-16.) Yet, Dr. Liversidge's testimony only

indicates what is now known about nanotechnology, not what was known in 2002 by a person of skill in the art.[19] *See In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371-72 (Fed. Cir. 2012) (noting that reasonable expectation of success is measured from the perspective of the person of ordinary skill in the art at the time of the invention (citing *Life Tech., Inc. v. Clontech Lab., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000))). There is no evidence to suggest a person of skill in the art, in 2002, would have believed anything other than that nanotechnology was sufficiently simple to apply and would result in the claimed benefits as TWi has shown with extensive evidence.

VI. Secondary Considerations

Before making its final conclusions with respect to obviousness, a court must consider any proffered objective indicia of nonobviousness. *In re Cyclobenzaprine*, 676 F.3d at 1079. Such evidence protects against inappropriate hindsight analysis and ensures the court considers obviousness only from the perspective of one skilled in the art at the time of invention. *Id.* Although the burden of persuasion never shifts away from the party challenging a patent's validity, *id.* at 1075 (finding the district court erred by shifting the burden of persuasion to the patentee on the issue of secondary considerations), the proponent of evidence of secondary considerations must establish a nexus between the evidence and the merits of the claimed invention, *In re Kao*, 639 F.3d at 1068. Further, the evidence must be commensurate with the scope of the claims, meaning, although the patentee does not have to demonstrate the existence

[19] For this reason, the court does not consider Par's evidence of specific failures with respect to nanoparticulate formulations of Clopidogrel, Orlistat, or Sorafenib persuasive evidence of what a person skilled in the art would have expected. There is either no evidence of when the attempts were made, (*see* DTX 47; DTX 49), or the attempts were made after 2002, (*see* DTX 48 (demonstrating attempts to create a nanoparticulate formulation of Orlistat in 2006)). Further, three examples of failure among many compounds does not show there is no reasonable expectation of success with other compounds. Obviousness only requires a reasonable expectation of success, not "absolute predictability." *In re Droge*, 694 F.3d 1334, 1338 (Fed. Cir. 2012) (quoting *In re Kubin*, 561 F.3d at 1360) (internal quotation marks omitted).

of the secondary indicia with respect to every embodiment of the claims, he does have to provide adequate evidence that other, untested embodiments falling within the claims would behave in the same manner. *Id.*

Par offers evidence of several secondary considerations of non-obviousness: unexpected results, long-felt but unmet need, copying, and commercial success. None of them sufficiently undermine a finding of obviousness.

A. Unexpected results

Unexpected results must be established by factual evidence, and the evidence must demonstrate the claimed invention exhibits some superior property or advantage that would have been surprising to one skilled in the art. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Par claims that the reduced food effect associated with Megace ES and the increased weight gain exhibited by patients to whom it was administered were unexpected. Even if the court were to find the reduced food effect and increased weight gain unexpected,[20] however, TWi has provided clear and convincing evidence that there were motivations in the art other than fed-fasted variability and the need for increased weight gain to use nanotechnology with the existing method and that the technology's ability to reduce interpatient variability and viscosity were known. The fact that the use of nanotechnology may have surprisingly solved other problems as well does not undermine that finding. *See Allergan*, 726 F.3d at 1293 (finding unexpected results with respect to one property did not overcome the prima facie showing of obviousness where there were other issues providing motivation to combine prior art elements).

[20] Although not necessary to its findings, the court notes that the improvements do not appear to be more than what might be predicted given the known improvements in efficacy associated with nanotechnology. *See In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (holding that unexpected results require a difference in kind, not merely degree (citing *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996))).

B. Long-Felt Need

Evidence of a long-felt, but unmet, need is probative of non-obviousness where it demonstrates that a demand existed for the invention and that others had previously tried but failed to meet the demand. *In re Cyclobenzaprine*, 676 F.3d at 1082. Dr. Wanke provided testimony that, in her experience working with HIV/AIDS patients, a long-standing need existed for a more effective means of returning patients to their normal weight. (Tr. 4:2 at 47:5-49:9.) According to Par, the pilot study comparing Megace ES and Megace OS in HIV/AIDS patients demonstrates that the claimed invention met that longstanding need because participants in the study taking Megace ES experienced "significantly greater weight gain." (PTX 94 at 209, fig. 1, 215.) All but four of the asserted claims (Claims 2, 10, 21, 24) disclose a method of increasing body mass in human patients without regard to whether the weight loss is associated with HIV/AIDS. Evidence of a long-felt need for superior weight gain in HIV/AIDS patients, and the claimed invention's ability to meet that need, is thus not commensurate with these claims. Par has offered no evidence to support a conclusion that other embodiments falling within the non-HIV/AIDS specific claims would meet a long-felt, but unmet, need in populations other than those with HIV/AIDS.[21] *See MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1264-65 (Fed. Cir. 2013); *In re Kao*, 639 F.3d at 1068.

With respect to the claims that are HIV/AIDS-specific, the proffered evidence is simply not sufficient to demonstrate that the claimed invention was in demand, i.e. that it met a long-felt need. Par claims the need was for a more effective means of returning patients to premorbid

[21] The parties' stipulation that Megace ES is an embodiment of the claims does not render Par's evidence of an unmet need with respect to the treatment of HIV/AIDS patients commensurate with the claims. The parties stipulated that Megace ES would "constitute *a* method claimed," not that it would constitute the only embodiment. (Stipulation Regarding Megace ES, ECF No. 174, ¶ 4(a) (emphasis added).)

weight. (*See* Pl.'s Brief at 36 (citing Tr. 4:2 at 47:14-49:9; PTX 143 at 565).) Yet, in the report of the study on which Par relies, researchers only conclude that "the use of the [Megace ES] formulation may be preferable to [Megace OS]." (PTX 94 at 215.) Although perhaps more effective, neither the study report nor Par provides evidence as to whether the superior efficacy of Megace ES was enough to meet the unmet need,[22] and the researchers' equivocal statement that it "may be" preferable is simply not enough to demonstrate that it was.

C. Copying

Par claims TWi's copying of Megace ES provides strong evidence of nonobviousness. Although copying often can provide evidence of nonobviousness, it cannot do so in this case. TWi was attempting to bring a generic version of Megace ES to market and copying in that context is not probative because FDA approval requires a showing of bioequivalence. *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013); *Purdue Pharma Products*, 377 F. App'x 978, 983 (Fed. Cir. 2010).[23]

D. Commercial Success

Commercial success can provide objective evidence of nonobviousness because "the law

[22] It should be noted that the court understands "significantly superior weight gain," as used in the study, to mean *statistically* significant superior weight gain. Par similarly claimed to understand it this way earlier in the litigation. (*See* Pl.'s Opp'n to Def.'s Mot., ECF No. 154, at 5.) The actual difference in mean weight gain between the two formulations was only ever, at most, two kilograms.

[23] Par claims the "ANDA exception" only applies when the FDA requires the filer to copy the invention. This is a misinterpretation of the Federal Circuit's holding. All ANDAs must demonstrate bioequivalence, either through a study or one of a limited number of alternatives. *See* 21 C.F.R. 320.20. The Federal Circuit held that, for that reason, copying is not compelling where it is in the context of an ANDA. *See Purdue Pharma Products L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 983 (Fed. Cir. 2010) ("[C]opying in the ANDA context is not probative of nonobviousness *because* a showing of bioequivalence is required for FDA approval." (emphasis added)); *see also Cephalon Inc. v. Mylan Pharm. Inc.*, -- F. Supp. 2d --, 2013 WL 3810858 at *26 (D. Del. 2013) (rejecting copying as valid evidence in the ANDA context without making a factual finding as to what the FDA required).

presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co. Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Commercial success is only significant, however, where there is a nexus between the novel aspects of the invention and the commercial success. *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013). The feature responsible for the commercial success must not have been known in the prior art. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006); *J.T. Eaton & Co., Inc. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). Where the patentee shows commercial success with a product that is an embodiment of the invention, a court presumes the commercial success is due to the novelty of the invention. *J.T. Eaton*, 106 F.3d at 1571. The burden is then on the challenger to demonstrate otherwise. *Id.*

Although the parties have stipulated that Megace ES is an embodiment of the invention, the presumption that all of its commercial success was due to novel features cannot stand. Par's marketing documents demonstrate that in addition to selling Megace ES on the basis of its reduced food effect, Par touted the reduced volume and viscosity of the formulation. (*See, e.g.*, PTX 241 at PAR-MEG150891; PTX 249 at PAR-MEG382865; PTX 449 at PAR-MEG100199). In fact, reduced dose volume and reduced viscosity were two of the three "core messages" used to sell the drug. (Pl.'s Brief at 40-41.) Some portion of the claimed success, therefore, may be due to features that were not novel: it was known in the prior art that using nanoparticles would reduce dose volumes and viscosity. Commercial success founded on non-novel features does not provide persuasive evidence of nonobviousness. *See Ormco*, 463 F.3d at 1312 ("[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent.").

Not only does the evidence suggest any success may stem from features of the drug other

than those that were novel, but Megace ES's market share and total sales figures do not provide evidence of commercial success sufficient to undermine a finding of obviousness. First, even assuming Par's expert, Dr. Vandaele, was correct that Megace ES held 19-23 percent of the market, (Tr. 5:1 at 53:21-22.) that leaves over 75 percent of the market still held by prior art products. In addition, 23 percent was the peak market share in 2007, two years after launch and after over $70 million was spent on marketing, (PTX 167 at 1), and it appears to have since declined to only 19 percent, (Tr. 5:1 at 62:6-12). In addition, the sales figures—$600 million in gross sales, $450 million in net sales, and over $100 million in aggregate operating profits, all over six years—and market share touted by Par must be discounted because, for the first four years the product was on the market, Par boosted its sales, at least to some degree,[24] by engaging in criminal conduct. (*See* Guilty Plea Transcript, DTX 247 at 15:13-16:1 (admitting that Par made false and/or misleading claims when it marketed Megace ES as having "superior clinical efficacy" over Megace OS despite lacking "adequate or sufficient data from well-controlled clinical trials" to support such claims).) After discounting sales and market share figures for Par's criminal conduct, and considering that some portion of sales may be due to the touting of non-novel features, the court does not find evidence of commercial success that persuasively undermines the claimed invention's obviousness.[25]

[24] It is somewhat difficult to assess what portion of sales or profits were due to Par's criminal conduct. In the plea agreement, Par and the Department of Justice agreed that Par received $11 million in pecuniary gain from its misbranded sales, (Plea Agreement, DTX 245, at 2), but Par ended up paying $45 or $46 million to settle the case, (Tr. 5:2 at 9:18-21).

[25] Par also claims that TWi's copying of Megace ES provides evidence of commercial success, but this argument is without merit. *See Galderma Labs, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) ("The mere fact that generic pharmaceutical companies seek approval to market a generic version of a drug, without more, is not evidence of commercial success that speaks to the non-obviousness of patent claims.")

CONCLUSION

For the foregoing reasons, the court finds that TWi has shown by clear and convincing evidence that the asserted claims of the '576 patent are invalid because they would have been obvious to a person of skill in the art at the time of invention. A separate Order follows.

February 21, 2014
Date

/s/
Catherine C. Blake
United States District Judge

US007101576B2

(12) **United States Patent**
Hovey et al.

(10) **Patent No.: US 7,101,576 B2**
(45) **Date of Patent: Sep. 5, 2006**

(54) **NANOPARTICULATE MEGESTROL FORMULATIONS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 374 days.

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A61K 9/10 (2006.01)
A61K 9/56 (2006.01)

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(58) **Field of Classification Search** 424/489, 424/400, 451, 464; 514/169
See application file for complete search history.

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(57) **ABSTRACT**

The present invention is directed to nanoparticulate compositions comprising megestrol. The megestrol particles of the composition have an effective average particle size of less than about 2000 nm.

31 Claims, 3 Drawing Sheets

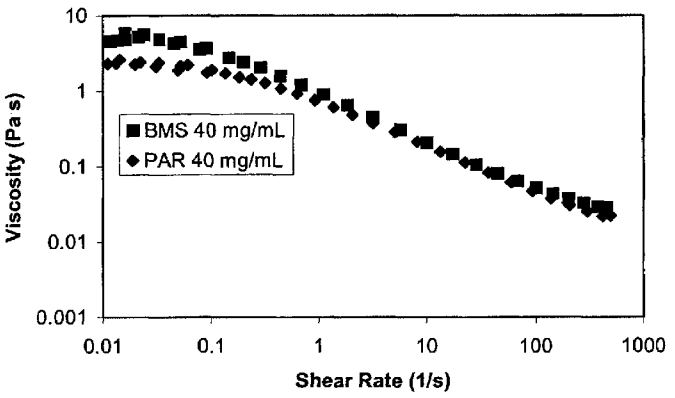

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FIGURE 1

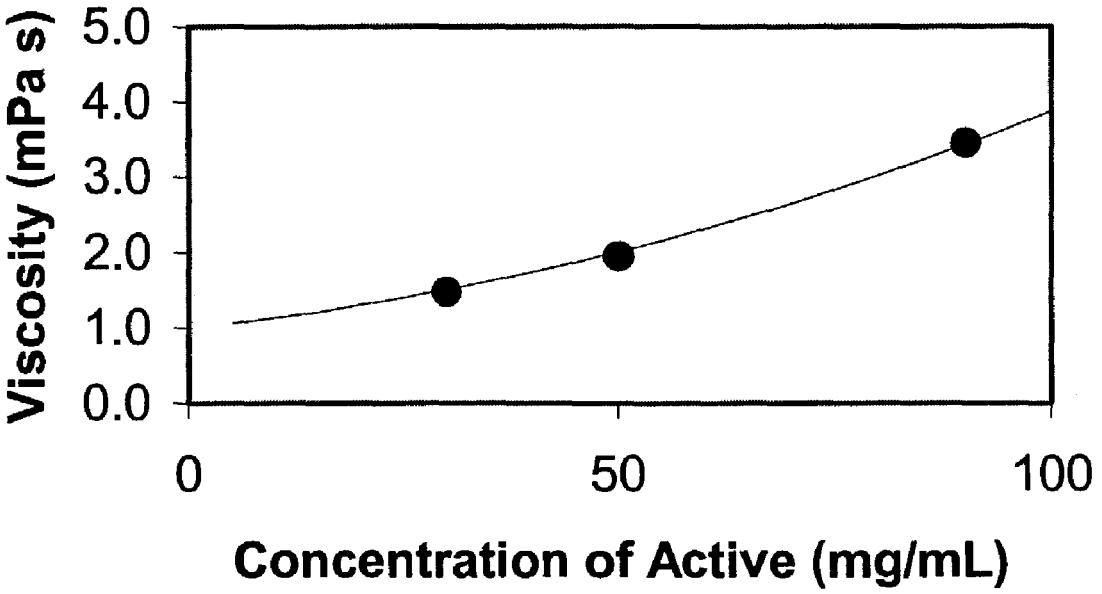

Viscosity (mPa s)
5.0
4.0
3.0
2.0
1.0
0.0
0
50
100
Concentration of Active (mg/mL)

FIGURE 2

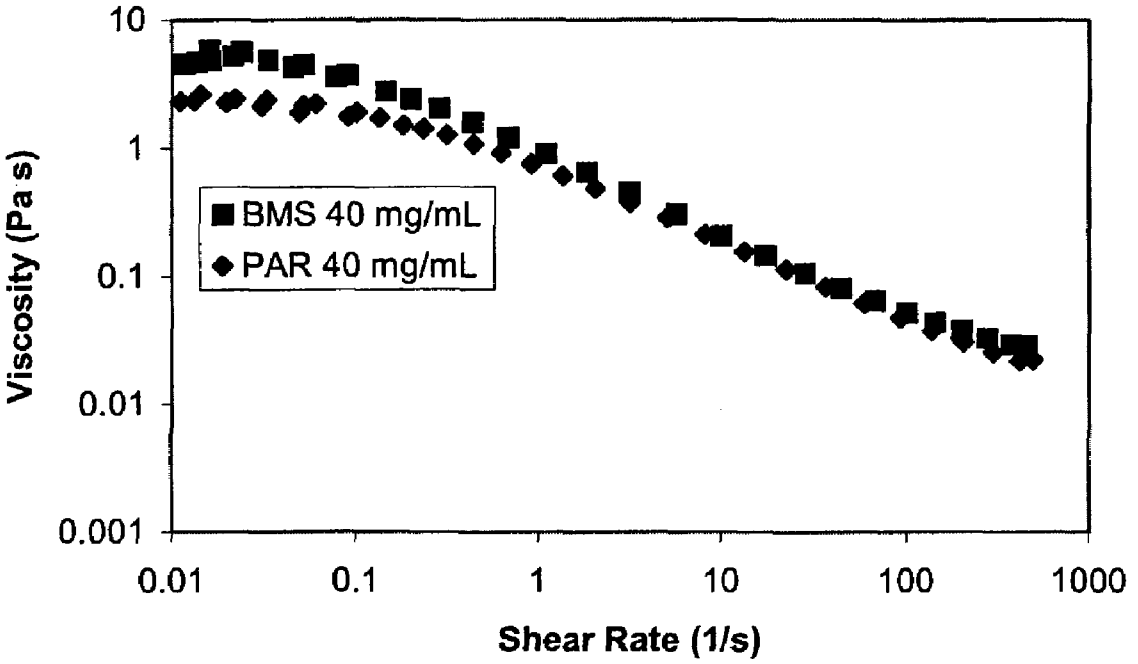
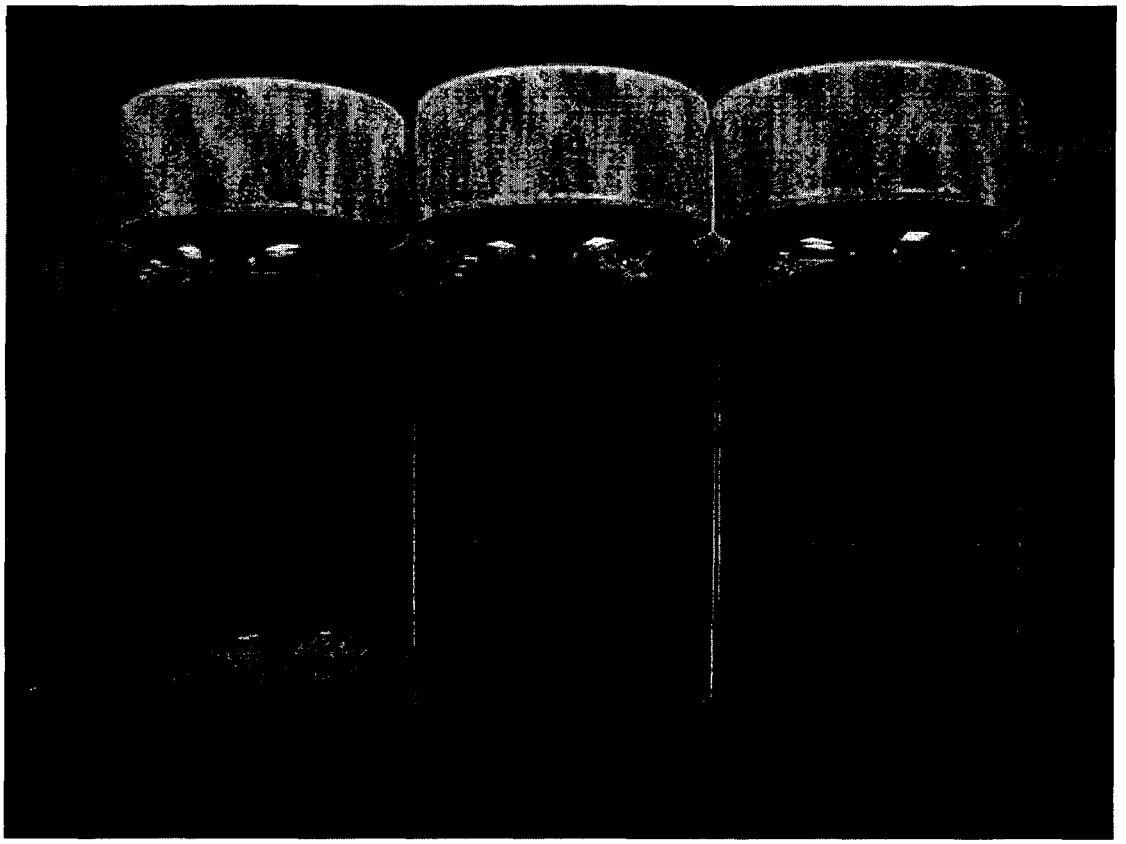

10
1
0.1
0.01
0.001
Viscosity (Pa s)
BMS 40 mg/mL
PAR 40 mg/mL
0.01
0.1
1
10
100
1000
Shear Rate (1/s)

FIGURE 3



NANOPARTICULATE MEGESTROL FORMULATIONS

FIELD OF THE INVENTION

The present invention relates to a nanoparticulate composition comprising megestrol and preferably at least one surface stabilizer associated with the surface of the drug. The nanoparticulate megestrol particles have an effective average particle size of less than about 2000 nm.

BACKGROUND OF THE INVENTION

A. Background Regarding Nanoparticulate Compositions

Nanoparticulate compositions, first described in U.S. Pat. No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto the surface thereof a non-crosslinked surface stabilizer. The '684 patent does not describe nanoparticulate compositions of megestrol.

Methods of making nanoparticulate compositions are described, for example, in U.S. Pat. Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Nanoparticulate compositions are also described, for example, in U.S. Pat. No. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" U.S. Pat. No. 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" U.S. Pat. No. 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" U.S. Pat. No. 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" U.S. Pat. No. 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" U.S. Pat. No. 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" U.S. Pat. No. 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,399,363 and U.S. Pat. No. 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" U.S. Pat. No. 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" U.S. Pat. No. 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" U.S. Pat. No. 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" U.S. Pat. No. 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,518,738 for "Nanoparticulate NSAID Formulations;" U.S. Pat. No. 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" U.S. Pat. No. 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,552,160 for "Surface Modified NSAID Nanoparticles;" U.S. Pat. No. 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" U.S. Pat. No. 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" U.S. Pat. No. 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" U.S. Pat. No. 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" U.S. Pat. No. 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" U.S. Pat. No. 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" U.S. Pat. No. 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" U.S. Pat. No. 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" U.S. Pat. No. 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" U.S. Pat. No. 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" U.S. Pat. No. 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,919 for "Nanoparticles Containing the R(−)Enantiomer of Ibuprofen;" U.S. Pat. No. 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" U.S. Pat. No. 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" U.S. Pat. No. 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" U.S. Pat. No. 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" U.S. Pat. No. 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" U.S. Pat. No. 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" U.S. Pat. No. 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" U.S. Pat. No. 6,270,806 for "Use of PEG-Deriva-

tized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" U.S. Pat. No. 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," U.S. Pat. No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," U.S. Pat. No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" U.S. Pat. No. 6,431,478 for "Small Scale Mill;" and U.S. Pat. No. 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," all of which are specifically incorporated by reference. In addition, U.S. patent application No. 20020012675 A1, published on Jan. 31, 2002, for "Controlled Release Nanoparticulate Compositions," describes nanoparticulate compositions, and is specifically incorporated by reference.

Amorphous small particle compositions are described, for example, in U.S. Pat. No. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" U.S. Pat. No. 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" U.S. Pat. No. 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" U.S. Pat. No. 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and U.S. Pat. No. 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

B. Background Regarding Megestrol

Megestrol acetate, also known as 17α-acetyloxy-6-methylpregna-4,6-diene-3,20-dione, is a synthetic progestin with progestational effects similar to those of progesterone. It is used in abortion, endometriosis, and menstrual disorders. It is also used in a variety of situations including treatment of breast cancer, contraception, and hormone replacement therapy in post-menopausal women. Megestrol acetate is also frequently prescribed as an appetite enhancer for patients in a wasting state, such as HIV wasting, cancer wasting, or anorexia. In combination with ethynyl estradiol it acts as an oral contraceptive. It is also administered to subjects after castration.

Megestrol acetate is marketed by Par Pharmaceuticals, Inc. and under the brand name Megace® by Bristol Myers Squibb Co. Typical commercial formulations are relatively large volume. For example, Par Pharmaceuticals, Inc. megestrol acetate oral suspension contains 40 mg of micronized megestrol acetate per ml, and the package insert recommends an initial adult dosage of megestrol acetate oral suspension of 800 mg/day (20 mL/day). The commercial formulations of megestrol acetate are highly viscous suspensions, which have a relatively long residence time in the mouth and any tubing. Highly viscous substances are not well accepted by patient populations, particularly patients suffering wasting and those that are intubated.

U.S. Pat. No. 6,028,065 for "Flocculated Suspension of Megestrol Acetate," assigned to Pharmaceutical Resources, Inc. (Spring Valley, N.Y.), describes oral pharmaceutical micronized megestrol acetate compositions in the form of a stable flocculated suspension in water. The compositions comprise at least one compound selected from the group consisting of polyethylene glycol, propylene glycol, glycerol, and sorbitol; and a surfactant, wherein polysorbate and polyethylene glycol are not simultaneously present. U.S. Pat. No. 6,268,356, also for "Flocculated Suspension of Megestrol Acetate," and assigned to Pharmaceutical Resources, Inc., describes methods of treating a neoplastic condition comprising administering the composition of U.S. Pat. No. 6,028,065.

Another company that has developed a megestrol formulation is Eurand (Milan, Italy). Eurand's formulation is a modified form of megestrol acetate having increased bioavailability. Eurand structurally modifies poorly soluble drugs to increase their bioavailability. See www.eurand-.com. For megestrol acetate, Eurand uses its' "Biorise" process, in which a New Physical Entity (NPE) is created by physically breaking down megestrol's crystal lattice. This results in drug nanocrystals and/or amorphous drug, which are then stabilized with biologically inert carriers. Eurand uses three types of carriers: swellable microparticles, composite swellable microparticles, and cyclodextrins. See e.g., http://www.eurand.com/page.php?id=39. Such a delivery system can be undesirable, as "breaking down" an active agent's crystalline structure can modify the activity of the active agent. A drug delivery system which does not alter the structure of the active agent is preferable.

Among the progestins, megestrol acetate is one of the few that can be administered orally because of its reduced first-pass (hepatic) metabolism, compared to the parent hormone. In addition, it is claimed to be superior to 19-nor compounds as an antifertility agent because it has less effect on the endometrium and vagina. See *Stedman 's Medical Dictionary,* 25th Ed., page 935 (Williams & Wilkins, MD 1990). There is a need in the art for megestrol formulations which exhibit increased bioavailability, less variability, and/or less viscosity as compared to conventional microparticulate megestrol formulations. The present invention satisfies these needs.

SUMMARY OF THE INVENTION

The invention relates to nanoparticulate megestrol compositions. The compositions comprise megestrol and preferably at least one surface stabilizer associated with the surface of the megestrol particles. The nanoparticulate megestrol particles have an effective average particle size of less than about 2000 nm.

Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate megestrol composition of the invention. The pharmaceutical compositions preferably comprise megestrol, at least one surface stabilizer, and a pharmaceutically acceptable carrier, as well as any desired excipients.

This invention further discloses a method of making a nanoparticulate megestrol composition according to the invention. Such a method comprises contacting megestrol particles and at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate megestrol composition. The one or more surface stabilizers can be contacted with megestrol either before, during, or after size reduction of the megestrol.

The present invention is also directed to methods of treatment using the nanoparticulate compositions of the invention for conditions such as endometriosis, dysmenorrhea, hirsutism, uterine bleeding, neoplastic diseases, methods of appetite enhancement, contraception, hormone replacement therapy, and treating patients following castration. Such methods comprises administering to a subject a therapeutically effective amount of a nanoparticulate megestrol composition according to the invention.

Finally, the present invention is directed to megestrol acetate compositions with improved physical (viscosity) and

pharmacokinetic profiles (such as less variability) over traditional forms of megestrol acetate.

Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**: Illustrates viscosity in units of mPa s as a function of concentration. Circles indicate the experimental values and the line illustrates the expected trend;

FIG. **2**: Illustrates viscosity in units of Pa s as a function of shear rate for two commercial samples, Bristol Myers Squibb and Par Pharmaceuticals, both at an active concentration of 40 mg/mL; and

FIG. **3**: Shows a photograph of, from left to right, a nanoparticulate dispersion of megestrol acetate, a commercial sample of megestrol acetate marketed by Par Pharmaceuticals, and a commercial sample of megestrol acetate marketed by Bristol Myers Squibb.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to nanoparticulate compositions comprising megestrol particles having an effective average particle size of less than about 2 microns. The compositions comprise megestrol and preferably at least one surface stabilizer associated with the surface of the drug.

As taught in the '684 patent, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition. It was surprisingly discovered that stable nanoparticulate megestrol compositions can be made.

For example, nanoparticulate megestrol compositions with hydroxypropyl methylcellulose (HPMC) and sodium lauryl sulfate (SLS) as surface stabilizers remained stable in an electrolyte solution mimicking the physiological pH of the stomach. Nanoparticulate megestrol compositions comprising HPMC and SLS are stable for several weeks at temperatures up to 40° C. with only minimal particle size growth. In addition, nanoparticulate megestrol compositions with hydroxypropylcellulose (HPC) and dioctyl sodium sulfosuccinate (DOSS) as surface stabilizers, HPMC and DOSS as surface stabilizers, polyvinylpyrrolidone (PVP) and DOSS as surface stabilizers, and Plasdone® S630 and DOSS as surface stabilizers were stable in electrolyte fluids and exhibited acceptable physical stability at 5° C. for 4 weeks. (Plasdone® S630 (ISP) is a random copolymer of vinyl acetate and vinyl pyrrolidone.) Moreover, the nanoparticulate megestrol/HPMC/SLS and nanoparticulate megestrol/HPMC/DOSS compositions also exhibited acceptable physical stability at 25° C. and 40° C. for 4 weeks.

Advantages of the nanoparticulate megestrol compositions of the invention include, but are not limited to: (1) low viscosity liquid nanoparticulate megestrol dosage forms; (2) for liquid nanoparticulate megestrol compositions having a low viscosity—better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (3) for liquid nanoparticulate megestrol compositions having a low viscosity—ease of dispensing because one can use a cup or a syringe; (4) faster onset of action; (5) smaller doses of megestrol required to obtain the same pharmacological effect as compared to conventional microcrystalline forms of megestrol; (6) increased bioavailability as compared to conventional microcrystalline forms of megestrol; (7) substantially similar pharmacokinetic profiles of the nanoparticulate megestrol compositions when administered in the fed versus the fasted state; (8) bioequivalency of the nanoparticulate megestrol compositions when administered in the fed versus the fasted state; (9) redispersibility of the nanoparticulate megestrol particles present in the compositions of the invention following administration; (10) bioadhesive nanoparticulate megestrol compositions; (11) improved pharmacokinetic profiles, such as more rapid megestrol absorption, greater megestrol absorption, and longer megestrol dose retention in the blood following administration; (12) the nanoparticulate megestrol compositions can be used in conjunction with other active agents; (13) the nanoparticulate megestrol compositions preferably exhibit an increased rate of dissolution as compared to conventional microcrystalline forms of megestrol; (14) improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher dose loading and smaller tablet or liquid dose volumes; (15) the nanoparticulate megestrol compositions are suitable for parenteral administration; (16) the nanoparticulate megestrol compositions can be sterile filtered; and (17) the nanoparticulate megestrol compositions do not require organic solvents or pH extremes.

The present invention is described herein using several definitions, as set forth below and throughout the application. "About" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which the term is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

As used herein with reference to stable drug particles, "stable" means that the megestrol particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise increase in particle size.

"Conventional active agents or drugs" refers to non-nanoparticulate compositions of active agents or solubilized active agents or drugs. Non-nanoparticulate active agents have an effective average particle size of greater than about 2 microns.

A. Preferred Characteristics of the Nanoparticulate Megestrol Compositions of the Invention

1. Low Viscosity

Typical commercial formulations of megestrol, such as Megace®, are relatively large volume, highly viscous substances that are not well accepted by patient populations, particularly subjects suffering from wasting. "Wasting" is a condition in which a subject finds it difficult to eat because, for example, food makes the subject nauseous. A highly viscous medicine is not compatible with treating such a condition, as frequently the highly viscous substance can cause additional nausea.

Moreover, viscous solutions can be problematic in parenteral administration because these solutions require a slow syringe push and can stick to tubing. In addition, conventional formulations of poorly water-soluble active agents, such as megestrol, tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with highly water-soluble substances.

Liquid dosage forms of the nanoparticulate megestrol compositions of the invention provide significant advantages over conventional liquid megestrol dosage forms. The

low viscosity and silky texture of liquid dosage forms of the nanoparticulate megestrol compositions of the invention results in advantages in both preparation and use. These advantages include, for example: (1) better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (2) ease of dispensing because one can use a cup or a syringe; (3) potential for formulating a higher concentration of megestrol resulting in a smaller dosage volume and thus less volume for the subject to consume; and (4) easier overall formulation concerns.

Liquid megestrol dosage forms which are easier to consume are especially important when considering juvenile patients, terminally ill patients, and patients suffering from gastrointestinal tract dysfunction or other conditions where nausea and vomiting are symptoms. For example, patients suffering from cancer or AIDS-related complications are commonly hypermetabolic and, at various stages of disease, exhibit gastrointestinal dysfunction. Additionally, drugs used to treat these conditions often cause nausea and vomiting. Viscous or gritty formulations, and those that require a relatively large dosage volume, are not well tolerated by patient populations suffering from wasting associated with these diseases because the formulations can exacerbate nausea and encourage vomiting.

The viscosities of liquid dosage forms of nanoparticulate megestrol according to the invention are preferably less than about 1/200, less than about 1/175, less than about 1/150, less than about 1/125, less than about 1/100, less than about 1/75, less than about 1/50, or less than about 1/25 of existing commercial liquid oral megestrol acetate compositions, e.g. Megace®, at about the same concentration per ml of megestrol.

Typically the viscosity of liquid nanoparticulate megestrol dosage forms of the invention is from about 175 mPa s to about 1 mPa s, from about 150 mPa s to about 1 mPa, from about 125 mPa s to about 1 mPa s, from about 100 mPa s to about 1 mPa s, from about 75 mPa s to about 1 mPa s, from about 50 mPa s to about 1 mPa s, from about 25 mPa s to about 1 mPa s, from about 15 mPa s to about 1 mPa s, or from about 5 mPa s to about 1 mPa s. Such a viscosity is much more attractive for subject consumption and may lead to better overall subject compliance.

Viscosity is concentration and temperature dependent. Typically, a higher concentration results in a higher viscosity, while a higher temperature results in a lower viscosity. Viscosity as defined above refers to measurements taken at about 20° C. (The viscosity of water at 20° C. is 1 mPa s.) The invention encompasses equivalent viscosities measured at different temperatures.

A viscosity of 1.5 mPa s for a nanoparticulate megestrol dispersion having a concentration of 30 mg/mL, measured at 20° C., was obtained by the inventors. An equivalent viscosity at 4% active agent concentration would be 1.7 mPa s. Higher and lower viscosities can be obtained by varying the temperature and concentration of megestrol.

Another important aspect of the invention is that the nanoparticulate megestrol compositions of the invention are not turbid. "Turbid," as used herein refers to the property of particulate matter that can be seen with the naked eye or that which can be felt as "gritty." The nanoparticulate megestrol compositions of the invention can be poured out of or extracted from a container as easily as water, whereas a conventional standard commercial (i.e., non-nanoparticulate or solubilized) megestrol liquid dosage form exhibits notably more "sluggish" characteristics.

The liquid formulations of this invention can be formulated for dosages in any volume but preferably equivalent or smaller volumes than existing commercial formulations.

2. Fast Onset of Activity

The use of conventional formulations of megestrol is not ideal due to delayed onset of action. In contrast, the nanoparticulate megestrol compositions of the invention exhibit faster therapeutic effects.

Preferably, following administration the nanoparticulate megestrol compositions of the invention have a T_{max} of less than about 5 hours, less than about 4.5 hours, less than about 4 hours, less than about 3.5 hours, less than about 3 hours, less than about 2.75 hours, less than about 2.5 hours, less than about 2.25 hours, less than about 2 hours, less than about 1.75 hours, less than about 1.5 hours, less than about 1.25 hours, less than about 1.0 hours, less than about 50 minutes, less than about 40 minutes, less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, or less than about 10 minutes.

3. Increased Bioavailability

The nanoparticulate megestrol compositions of the invention preferably exhibit increased bioavailability and require smaller doses as compared to prior conventional megestrol compositions administered at the same dose.

Any drug, including megestrol, can have adverse side effects. Thus, lower doses of megestrol which can achieve the same or better therapeutic effects as those observed with larger doses of conventional megestrol compositions are desired. Such lower doses can be realized with the nanoparticulate megestrol compositions of the invention because the greater bioavailability observed with the nanoparticulate megestrol compositions as compared to conventional drug formulations means that smaller does of drug are required to obtain the desired therapeutic effect. Specifically, a once a day dose of about 375 mg/5 mL (75 mg/mL) of a nanoparticulate megestrol acetate composition is considered equivalent to an 800 mg dose of Megace®.

Administration of nanoparticulate megestrol formulations of the present invention can exhibit bioavailability, as determined by AUC0-t, in an amount of about 3000 ng hr/ml to about 10,000 ng hr/ml, wherein C_{max} is about 300 ng/ml to about 1100 ng/ml in a fed human subject and AUC0-t in an amount of about 2000 ng hr/ml to about 9000 ng hr/ml, wherein C_{max} is about 300 ng/ml to about 2000 ng/ml in a fasted human subject. Preferably, nanoparticulate megestrol formulations of the present invention exhibit comparable bioavailability in a range of between about 75 and about 130%, more preferably between about 80% and about 125%, of the specified therapeutic parameter (e.g., AUC0-t or C_{max}).

4. The Pharmacokinetic Profiles of the Nanoparticulate Megestrol Compositions of the Invention are not Substantially Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

The invention encompasses nanoparticulate megestrol compositions wherein the phannacokinetic profile of the megestrol is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is no substantial difference in the quantity of megestrol absorbed or the rate of megestrol absorption when the nanoparticulate megestrol compositions are administered in the fed versus the fasted state. Thus, the nanoparticulate megestrol compositions of the invention substantially eliminate the effect of food on the pharmacokinetics of megestrol.

The difference in absorption of the nanoparticulate megestrol composition of the invention, when administered in the fed versus the fasted state, is less than about 35%, less than about 30%, less than about 25%, less than about 20%, less

than about 15%, less than about 10%, less than about 5%, or less than about 3%. This is an especially important feature in treating patients with difficulty in maintaining a fed state.

In addition, preferably the difference in the rate of absorption (i.e., T_{max}) of the nanoparticulate megestrol compositions of the invention, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 3%, or essentially no difference.

Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food.

5. Redispersibility Profiles of the Nanoparticulate Megestrol Compositions of the Invention

An additional feature of the nanoparticulate megestrol compositions of the invention is that the compositions redisperse such that the effective average particle size of the redispersed megestrol particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate megestrol particles present in the compositions of the invention did not redisperse to a substantially nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating megestrol into a nanoparticulate particle size.

This is because nanoparticulate megestrol compositions benefit from the small particle size of megestrol; if the nanoparticulate megestrol particles do not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated megestrol particles are formed. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall.

Preferably, the redispersed megestrol particles of the invention have an effective average particle size, by weight, of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

Moreover, the nanoparticulate megestrol compositions of the invention exhibit dramatic redispersion of the nanoparticulate megestrol particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution in a biorelevant aqueous media. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength.

Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1 M while fasted state intestinal fluid has an ionic strength of about 0.14. See e.g., Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," *Pharm. Res.,* 14 (4): 497–502 (1997).

It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (i.e., weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, etc.

Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 M HCl or less, about 0.01 M HCl or less, about 0.001 M HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

Electrolyte concentrations of 0.001 M HCl, 0.01 M HCl, and 0.1 M HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 M HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts+sodium, potassium and calcium salts of chloride, acetic acid/acetate salts+sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts+sodium, potassium and calcium salts of chloride, and citric acid/citrate salts+sodium, potassium and calcium salts of chloride.

6. Bioadhesive Nanoparticulate Megestrol Compositions

Bioadhesive nanoparticulate megestrol compositions of the invention comprise at least one cationic surface stabilizer, which are described in more detail below. Bioadhesive formulations of megestrol exhibit exceptional bioadhesion to biological surfaces, such as mucous.

In the case of bioadhesive nanoparticulate megestrol compositions, the term "bioadhesion" is used to describe the adhesion between the nanoparticulate megestrol compositions and a biological substrate (i.e. gastrointestinal mucin, lung tissue, nasal mucosa, etc.). See e.g., U.S. Pat. No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers," which is specifically incorporated by reference.

The bioadhesive megestrol compositions of the invention are useful in any situation in which it is desirable to apply the compositions to a biological surface. The bioadhesive megestrol compositions coat the targeted surface in a continuous and uniform film which is invisible to the naked human eye.

A bioadhesive nanoparticulate megestrol composition slows the transit of the composition, and some megestrol particles would also most likely adhere to tissue other than

the mucous cells and therefore give a prolonged exposure to megestrol, thereby increasing absorption and the bioavailability of the administered dosage.

7. Pharmacokinetic Profiles of the Nanoparticulate Megestrol Compositions of the Invention

The present invention also provides compositions of nanoparticulate megestrol having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the nanoparticulate megestrol compositions comprise the parameters: (1) that the T_{max} of megestrol, when assayed in the plasma of the mammalian subject, is less than about 5 hours; and (2) a C_{max} of megestrol is greater than about 30 ng/ml. Preferably, the T_{max} parameter of the pharmacokinetic profile is not greater than about 3 hours. Most preferably, the T_{max} parameter of the pharmacokinetic profile is not greater than about 2 hours.

The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of megestrol. For example, in a subject receiving 40 mg of megestrol four times a day, the T_{max} and C_{max} after the initial dose must be less than about 5 hours and greater than about 30 ng/ml, respectively. The compositions can be formulated in any way as described below.

Current formulations of megestrol include oral suspensions and tablets. According to the package insert of Megace®, the pharmacokinetic profile of the oral suspension contains parameters such that the median T_{max} is 5 hours and the mean C_{max} is 753 ng/ml. Further, the T_{max} and C_{max} for the Megace® 40 mg tablet, after the initial dose, is 2.2 hours and 27.6 ng/ml, respectively. *Physicians Desk Reference,* 55th Ed., 2001. The nanoparticulate megestrol compositions of the invention simultaneously improve upon at least the T_{max} and C_{max} parameters of the pharmacokinetic profile of megestrol.

In one embodiment, a threshold blood plasma concentration of megestrol of about 700 ng/ml is attained in less than about 5 hours after administration of the formulation, and preferably not greater than about 3 hours.

Preferably, the T_{max} of an administered dose of a nanoparticulate megestrol composition is less than that of a conventional standard commercial non-nanoparticulate megestrol composition, administered at the same dosage. In addition, preferably the C_{max} of a nanoparticulate megestrol composition is greater than the C_{max} of a conventional standard commercial non-nanoparticulate megestrol composition, administered at the same dosage.

A preferred nanoparticulate megestrol composition of the invention exhibits in comparative pharmacokinetic testing with a standard commercial formulation of megestrol, such as Megace® oral suspension or tablet from Bristol Myers Squibb, a T_{max} which is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, or less than about 10% of the T_{max} exhibited by the standard commercial formulation of megestrol.

A preferred nanoparticulate megestrol composition of the invention exhibits in comparative pharmacokinetic testing with a standard commercial formulation of megestrol, such as Megace® oral suspension or tablet from Bristol Myers Squibb, a C_{max} which is greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, or greater than about 150% than the C_{max} exhibited by the standard commercial formulation of megestrol.

There is no critical upper limit of blood plasma concentration so long as the dosage amounts set out below are not significantly exceeded. A suitable dose of megestrol, administered according to the method of the invention, is typically in the range of about 1 mg/day to about 1000 mg/day, or from about 40 mg/day to about 800 mg/day. Preferably, the therapeutically effective amount of the nanoparticulate megestrol compositions of the invention is ⅙, ⅕, ¼, ⅓rd, or ½ of the therapeutically effective amount of existing commercial megestrol formulations.

Any standard pharmacokinetic protocol can be used to determine blood plasma concentration profile in humans following administration of a nanoparticulate megestrol composition, and thereby establish whether that composition meets the pharmacokinetic criteria set out herein. For example, a randomized single-dose crossover study can be performed using a group of healthy adult human subjects. The number of subjects should be sufficient to provide adequate control of variation in a statistical analysis, and is typically about 10 or greater, although for certain purposes a smaller group can suffice. Each subject receives by oral administration at time zero a single dose (e.g., 300 mg) of a test formulation of megestrol, normally at around 8 am following an overnight fast. The subjects continue to fast and remain in an upright position for about 4 hours after administration of the megestrol formulation. Blood samples are collected from each subject prior to administration (e.g., 15 minutes) and at several intervals after administration. For the present purpose it is preferred to take several samples within the first hour, and to sample less frequently thereafter. Illustratively, blood samples could be collected at 15, 30, 45, 60, and 90 minutes after administration, then every hour from 2 to 10 hours after administration. Additional blood samples may also be taken later, for example at 12 and 24 hours after administration. If the same subjects are to be used for study of a second test formulation, a period of at least 7 days should elapse before administration of the second formulation. Plasma is separated from the blood samples by centrifugation and the separated plasma is analyzed for megestrol by a validated high performance liquid chromatography (HPLC) procedure, such as for example Garver et al., *J. Pharm. Sci.* 74(6):664–667 (1985), the entirety of which is hereby incorporated by reference. Plasma concentrations of megestrol referenced herein are intended to mean total megestrol concentrations including both free and bound megestrol.

Any formulation giving the desired pharmacokinetic profile is suitable for administration according to the present methods. Exemplary types of formulations giving such profiles are liquid dispersions and solid dose forms of nanoparticulate megestrol. Dispersions of megestrol have proven to be stable at temperatures up to 50° C. If the liquid dispersion medium is one in which the nanoparticulate megestrol has very low solubility, the nanoparticulate megestrol particles are present as suspended particles. The smaller the megestrol particles, the higher the probability that the formulation will exhibit the desired pharmacokinetic profile.

8. Combination Pharmacokinetic Profile Compositions

In yet another embodiment of the invention, a first nanoparticulate megestrol composition providing a desired pharmacokinetic profile is co-administered, sequentially admin-

istered, or combined with at least one other megestrol composition that generates a desired different pharmacokinetic profile. More than two megestrol compositions can be co-administered, sequentially administered, or combined. While the first megestrol composition has a nanoparticulate particle size, the additional one or more megestrol compositions can be nanoparticulate, solubilized, or have a conventional microparticulate particle size.

For example, a first megestrol composition can have a nanoparticulate particle size, conferring a short T_{max} and typically a higher C_{max}. This first megestrol composition can be combined, co-administered, or sequentially administered with a second composition comprising: (1) megestrol having a larger (but still nanoparticulate as defined herein) particle size, and therefore exhibiting slower absorption, a longer T_{max}, and typically a lower C_{max}; or (2) a microparticulate or solubilized megestrol composition, exhibiting a longer T_{max}, and typically a lower C_{max}.

The second, third, fourth, etc., megestrol compositions can differ from the first, and from each other, for example: (1) in the effective average particle sizes of megestrol; or (2) in the dosage of megestrol. Such a combination composition can reduce the dose frequency required.

If the second megestrol composition has a nanoparticulate particle size, then preferably the megestrol particles of the second composition have at least one surface stabilizer associated with the surface of the drug particles. The one or more surface stabilizers can be the same as or different from the surface stabilizer(s) present in the first megestrol composition.

Preferably where co-administration of a "fast-acting" formulation and a "longer-lasting" formulation is desired, the two formulations are combined within a single composition, for example a dual-release composition.

9. Combination Active Agent Compositions

The invention encompasses the nanoparticulate megestrol compositions of the invention formulated or co-administered with one or more non-megestrol active agents, which are either conventional (solubilized or microparticulate) or nanoparticulate. Methods of using such combination compositions are also encompassed by the invention. The non-megestrol active agents can be present in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

The compound to be administered in combination with a nanoparticulate megestrol composition of the invention can be formulated separately from the nanoparticulate megestrol composition or co-formulated with the nanoparticulate megestrol composition. Where a nanoparticulate megestrol composition is co-formulated with a second active agent, the second active agent can be formulated in any suitable manner, such as immediate-release, rapid-onset, sustained-release, or dual-release form.

If the non-megestrol active agent has a nanoparticulate particle size i.e., a particle size of less than about 2 microns, then preferably it will have one or more surface stabilizers associated with the surface of the active agent. In addition, if the active agent has a nanoparticulate particle size, then it is preferably poorly soluble and dispersible in at least one liquid dispersion media. By "poorly soluble" it is meant that the active agent has a solubility in a liquid dispersion media of less than about 30 mg/mL, less than about 20 mg/mL, less than about 10 mg/mL, or less than about 1 mg/mL. Useful liquid dispersion medias include, but are not limited to, water, aqueous salt solutions, safflower oil, and solvents such as ethanol, t-butanol, hexane, and glycol.

Such non-megestrol active agents can be, for example, a therapeutic agent. A therapeutic agent can be a pharmaceutical agent, including biologics. The active agent can be selected from a variety of known classes of drugs, including, for example, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, such as NSAIDs and COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives (hypnotics and neuroleptics), astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (anti-parkinsonian agents), haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

A description of these classes of active agents and a listing of species within each class can be found in Martindale's *The Extra Pharmacopoeia,* 31st Edition (The Pharmaceutical Press, London, 1996), specifically incorporated by reference. The active agents are commercially available and/or can be prepared by techniques known in the art.

Exemplary nutraceuticals and dietary supplements are disclosed, for example, in Roberts et al., *Nutraceuticals: The Complete Encyclopedia of Supplements, Herbs, Vitamins, and Healing Foods* (American Nutraceutical Association, 2001), which is specifically incorporated by reference. Dietary supplements and nutraceuticals are also disclosed in *Physicians' Desk Reference for Nutritional Supplements,* 1st Ed. (2001) and *The Physicians' Desk Reference for Herbal Medicines,* 1st Ed. (2001), both of which are also incorporated by reference. A nutraceutical or dietary supplement, also known as a phytochemical or functional food, is generally any one of a class of dietary supplements, vitamins, minerals, herbs, or healing foods that have medical or pharmaceutical effects on the body.

Exemplary nutraceuticals or dietary supplements include, but are not limited to, lutein, folic acid, fatty acids (e.g., DHA and ARA), fruit and vegetable extracts, vitamin and mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids (e.g., arginine, iso-leucine, leucine, lysine, methionine, phenylanine, threonine, tryptophan, and valine), green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics. Nutraceuticals and dietary supplements also include bio-engineered foods genetically engineered to have a desired property, also known as "pharmafoods."

10. Sterile Filtered Nanoparticulate Megestrol Compositions

The nanoparticulate megestrol compositions of the invention can be sterile filtered. This obviates the need for heat sterilization, which can harm or degrade megestrol, as well as result in crystal growth and particle aggregation.

Sterile filtration can be difficult because of the required small particle size of the composition. Filtration is an effective method for sterilizing homogeneous solutions when the membrane filter pore size is less than or equal to about 0.2 microns (200 nm) because a 0.2 micron filter is sufficient to remove essentially all bacteria. Sterile filtration is normally not used to sterilize conventional suspensions of micron-sized megestrol because the megestrol particles are too large to pass through the membrane pores.

A sterile nanoparticulate megestrol dosage form is particularly useful in treating immunocompromised patients, infants or juvenile patients, and the elderly, as these patient groups are the most susceptible to infection caused by a non-sterile liquid dosage form.

Because the nanoparticulate megestrol compositions of the invention can be sterile filtered, and because the compositions can have a very small megestrol effective average particle size, the compositions are suitable for parenteral administration.

11. Miscellaneous Benefits of the Nanoparticulate Megestrol Compositions of the Invention

The nanoparticulate megestrol compositions preferably exhibit an increased rate of dissolution as compared to conventional microcrystalline forms of megestrol. In addition, the compositions of the invention exhibit improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher dose loading and smaller tablet or liquid dose volumes. Moreover, the nanoparticulate megestrol compositions of the invention do not require organic solvents or pH extremes.

Another benefit of the nanoparticulate megestrol compositions of the invention is that is was surprisingly discovered that upon administration, nanoparticulate compositions of megestrol acetate reach therapeutic blood levels within one dose. This is in dramatic contrast to the current commercially available megestrol acetate composition (Megace® by Bristol Myers Squibb Co.), which requires multiple doses, administered over several days to a week, to build up to a therapeutic level of drug in the blood stream.

B. Compositions The invention provides compositions comprising nanoparticulate megestrol particles and preferably at least one surface stabilizer. The one or more surface stabilizers are preferably associated with the surface of the megestrol particles. Surface stabilizers useful herein preferably do not chemically react with the megestrol particles or itself. Individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

The present invention also includes nanoparticulate megestrol compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (e.g., intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracistemal, intraperitoneal, or topical administration, and the like.

1. Megestrol Particles

As used herein the term megestrol, which is the active ingredient in the composition, is used to mean megestrol, megestrol acetate (17α-acetyloxy-6-methylpregna-4,6-diene-3,20-dione), or a salt thereof. The megestrol particles can be present in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

Megestrol acetate is well known in the art and is readily recognized by one of ordinary skill. Generally, megestrol is used for treating breast cancer, endometrial cancer and, less frequently, prostate cancer. Megestrol is also frequently used as an appetite stimulant for patients in a wasting state, such as HIV wasting, cancer wasting, and anorexia. Megestrol may be used for other indications where progestins are typically used, such as hormone replacement therapy in post-menopausal women and oral contraception. Further, megestrol may be used for ovarian suppression in several conditions such as endometriosis, hirsutism, dysmenorrhea, and uterine bleeding, as well as uterine cancer, cervical cancer, and renal cancer. Megestrol is also used in patients following castration.

2. Surface Stabilizers

The choice of a surface stabilizer for megestrol is non-trivial. Accordingly, the present invention is directed to the surprising discovery that nanoparticulate megestrol compositions can be made.

Combinations of more than one surface stabilizer can be used in the invention. Preferred surface stabilizers include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, random copolymers of vinyl pyrrolidone and vinyl acetate, sodium lauryl sulfate, dioctylsulfosuccinate or a combination thereof. Preferred primary surface stabilizers include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, random copolymers of vinyl pyrrolidone and vinyl acetate, or a combination thereof. Preferred secondary surface stabilizers include, but are not limited to, sodium lauryl sulfate and dioctylsulfosuccinate.

Other surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Surface stabilizers include nonionic, cationic, ionic, and zwitterionic surfactants.

Representative examples of surface stabilizers include hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens such as e.g., Tween 20® and Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (e.g., Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (e.g., Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation),

Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-10G® or Surfactant 10-G® (Olin Chemicals, Stamford, Conn.); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)—CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammonium-bromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry,* (Marcel Dekker, 1990).

Particularly preferred nonpolymeric primary stabilizers are any nonpolymeric compound, such benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

(i) none of R_1R_4 are CH_3;
(ii) one of R_1–R_4 is CH_3;
(iii) three of R_1–R_4 are CH_3;
(iv) all of R_1–R_4 are CH_3;
(v) two of R_1–R_4 are CH_3, one of R_1–R_4 is $C_6H_5CH_2$, and one of R_1–R_4 is an alkyl chain of seven carbon atoms or less;
(vi) two of R_1–R_4 are CH_3, one of R_1–R_4 is $C_6H_5CH_2$, and one of R_1–R_4 is an alkyl chain of nineteen carbon atoms or more;
(vii) two of R_1–R_4 are CH_3 and one of R_1–R_4 is the group $C_6H_5(CH_2)_n$, where n>1;
(viii) two of R_1–R_4 are CH_3, one of R_1–R_4 is $C_6H_5CH_2$, and one of R_1–R_4 comprises at least one heteroatom;
(ix) two of R_1–R_4 are CH_3, one of R_1–R_4 is $C_6H_5CH_2$, and one of R_1–R_4 comprises at least one halogen;
(x) two of R_1–R_4 are CH_3, one of R_1–R_4 is $C_6H_5CH_2$, and one of R_1–R_4 comprises at least one cyclic fragment;
(xi) two of R_1–R_4 are CH_3 and one of R_1–R_4 is a phenyl ring; or
(xii) two of R_1–R_4 are CH_3 and two of R_1–R_4 are purely aliphatic fragments.

Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium

chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference. The surface stabilizers are commercially available and/or can be prepared by techniques known in the art.

3. Other Pharmaceutical Excipients

Pharmaceutical megestrol compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acsulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

4. Nanoparticulate Megestrol or Active Agent Particle Size

As used herein, particle size is determined on the basis of the weight average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, and disk centrifugation.

The compositions of the invention comprise nanoparticulate megestrol particles which have an effective average particle size of less than about 2000 nm (i.e., 2 microns). In other embodiments of the invention, the megestrol particles have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, when measured by the above techniques.

If the nanoparticulate megestrol composition additionally comprises one or more non-megestrol nanoparticulate active agents, then such active agents have an effective average particle size of less than about 2000 nm (i.e., 2 microns). In other embodiments of the invention, the nanoparticulate non-megestrol active agents can have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the nanoparticulate megestrol or nanoparticulate non-megestrol active agent particles have a particle size of less than about 2000 nm, by weight, when measured by the above-noted techniques. Preferably, at least about 70%, about 90%, about 95%, or about 99% of the nanoparticulate megestrol or nanoparticulate non-megestrol active agent particles have a particle size of less than the effective average, i.e., less than about 2000 nm, less than about 1900 nm, less than about 1800 nm, etc.

If the nanoparticulate megestrol composition is combined with a conventional or microparticulate megestrol composition or non-megestrol active agent composition, then such a composition is either solubilized or has an effective average particle size of greater than about 2 microns. By "an effective average particle size of greater than about 2 microns" it is meant that at least 50% of the conventional megestrol or non-megestrol active agent particles have a particle size of greater than about 2 microns, by weight,

when measured by the above-noted techniques. In other embodiments of the invention, at least about 70%, about 90%, about 95%, or about 99% of the conventional megestrol or non-megestrol active agent particles have a particle size greater than about 2 microns.

5. Concentration of Nanoparticulate Megestrol and Surface Stabilizers

The relative amounts of nanoparticulate megestrol and one or more surface stabilizers can vary widely. The optimal amount of the individual components can depend, for example, the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer, etc.

The concentration of megestrol can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined dry weight of the megestrol and at least one surface stabilizer, not including other excipients.

The concentration of the at least one surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the megestrol and at least one surface stabilizer, not including other excipients.

If a combination of two or more surface stabilizers is employed in the composition, the concentration of the at least one primary surface stabilizer can vary from about 0.01% to about 99.5%, from about 0.1% to about 95%, or from about 0.5% to about 90%, by weight, based on the total combined dry weight of the megestrol, at least one primary surface stabilizer, and at least one secondary surface stabilizer, not including other excipients. In addition, the concentration of the at least one secondary surface stabilizer can vary from about 0.01% to about 99.5%, from about 0.1% to about 95%, or from about 0.5% to about 90%, by weight, based on the total combined dry weight of the megestrol, at least one primary surface stabilizer, and at least one secondary surface stabilizer, not including other excipients.

C. Methods of Making Nanoparticulate Megestrol Compositions

The nanoparticulate megestrol compositions can be made using, for example, milling, homogenization, or precipitation techniques. Exemplary methods of making nanoparticulate compositions are described in the '684 patent.

Methods of making nanoparticulate compositions are also described in U.S. Pat. No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,665,331 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Pat. No. 5,662,883 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Pat. No. 5,560,932 for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

The resultant nanoparticulate megestrol compositions can be utilized in solid or liquid dosage formulations, such as controlled release formulations, solid dose fast melt formulations, aerosol formulations, lyophilized formulations, tablets, capsules, etc.

1. Milling to Obtain Nanoparticulate Megestrol Dispersions

Milling megestrol to obtain a nanoparticulate megestrol dispersion comprises dispersing megestrol particles in a liquid dispersion medium in which megestrol is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of megestrol to the desired effective average particle size. The dispersion medium can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol.

The megestrol particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the megestrol particles can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the megestrol/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

2. Precipitation to Obtain Nanoparticulate Megestrol Compositions

Another method of forming the desired nanoparticulate megestrol composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving megestrol in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

3. Homogenization to Obtain_Nanoparticulate Megestrol Compositions

Exemplary homogenization methods of preparing nanoparticulate active agent compositions are described in U.S. Pat. No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Such a method comprises dispersing megestrol particles in a liquid dispersion medium, followed by subjecting the dispersion to homogenization to reduce the particle size of the megestrol to the desired effective average particle size. The megestrol particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the megestrol particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the megestrol/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

D. Methods of Using Nanoparticulate Megestrol Formulations of the Invention

1. Applications of the Nanoparticulate Compositions of the Invention

The nanoparticulate megestrol compositions of the invention may be used as an appetite stimulant to treat wasting conditions or cachexia. As used herein, the term "wasting"

is used to mean a condition where the patient is losing body mass as a side effect of a disease progression, a disease treatment, or other condition. Examples of conditions where wasting is prevalent include, but are not limited to, HIV or AIDS, cancer, cachexia and anorexia.

Additional conditions where the nanoparticulate megestrol compositions of the invention may be used include, but are not limited to, neoplastic diseases where the disease normally regresses or the patient's symptoms are normally reduced in response to megestrol, or any other progestin.

The nanoparticulate megestrol compositions of the invention may also be used to treat conditions such as breast cancer, endometrial cancer, uterine cancer, cervical cancer, prostate cancer, and renal cancer. As used herein, the term "cancer" is used as one of ordinary skill in the art would recognize the term. Examples of cancers include, but are not limited to, neoplasias (or neoplasms), hyperplasias, dysplasias, metaplasias, and hypertrophies. The neoplasms may be benign or malignant, and they may originate from any cell type, including but not limited to epithelial cells of various origin, muscle cells, and endothelial cells.

The present invention also provides methods of hormone replacement therapy in post-menopausal women, or in subjects after castration, comprising administering a nanoparticulate megestrol composition of the invention. Further, the compositions of the present invention may be used for ovarian suppression in several situations such as endometriosis, hirsutism, dysmenorrhea, and uterine bleeding.

The present invention also provides methods of oral contraception comprising administering a nanoparticulate megestrol composition of the invention. In one embodiment, the compositions of the invention are administered in combination with estrogen or a synthetic estrogen.

2. Dosage Forms of the Invention

The nanoparticulate megestrol compositions of the invention can be administered to a subject via any conventional means including, but not limited to, orally, rectally, ocularly, parenterally (e.g., intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (e.g., powders, ointments or drops), or as a buccal or nasal spray. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

Moreover, the nanoparticulate megestrol compositions of the invention can be formulated into any suitable dosage form, including but not limited to liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

Nanoparticulate megestrol compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

The nanoparticulate megestrol compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Liquid nanoparticulate megestrol dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to megestrol, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

3. Dosage Quantities for the Nanoparticulate Megestrol Compositions of the Invention

The present invention provides a method of achieving therapeutically effective plasma levels of megestrol in a subject at a lower dose than the standard commercial formulations. This can permit smaller dosing volumes depending on the megestrol concentration chosen. Such a method comprises orally administering to a subject an effective amount of a nanoparticulate megestrol composition.

The nanoparticulate megestrol composition, when tested in fasting subjects in accordance with standard pharmacokinetic practice, produces a maximum blood plasma concentration profile of megestrol of greater than about 30 ng/ml in less than about 5 hours after the initial dose of the composition.

As used herein, the phrase "maximum plasma concentration" is interpreted as the maximum plasma concentration that megestrol will reach in fasting subjects.

A suitable dose of megestrol, administered according to the method of the invention, is typically in the range of about 1 mg/day to about 1000 mg/day, or from about 40 mg/day to about 800 mg/day. Preferably, the therapeutically effective amount of the megestrol of this invention is about ⅙, about ⅕, about ¼, about ⅓rd, or about ½ of the therapeutically effective amount of existing commercial megestrol formulations, e.g., Megace®g. "Therapeutically effective amount" as used herein with respect to a drug dosage, shall mean that dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that "therapeutically effective amount," administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a "therapeutically effective amount" by those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

One of ordinary skill will appreciate that effective amounts of megestrol can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of megestrol in the nanoparticulate compositions of the invention may be varied to obtain an amount of megestrol that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the administered megestrol, the desired duration of treatment, and other factors.

Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. Throughout the specification, any and all references to a publicly available document, including a U.S. patent, are specifically incorporated by reference.

In the examples that follow, the value for D50 is the particle size below which 50% of the megestrol particles fall. Similarly, D90 is the particle size below which 90% of the megestrol particles fall.

The formulations in the examples that follow were also investigated using a light microscope. Here, "stable" nanoparticulate dispersions (uniform Brownian motion) were readily distinguishable from "aggregated" dispersions (relatively large, nonuniform particles without motion). Stable, as known in the art and used herein, means the particles don't substantially aggregate or ripen (increase in fundamental particle size).

EXAMPLE 1

The purpose of this example was to describe preparation of nanoparticulate dispersions of megestrol acetate.

Formulations 1, 2, 3, 4 and 5, shown in Table 1, were milled under high energy Milling conditions using a NanoMill® (Elan Drug Delivery, Inc.) (see e.g., WO 00/72973 for "Small-Scale Mill and Method Thereof") and a Dyno®-Mill (Willy Bachofen AG).

TABLE 1

Formulation	Quantity of Megestrol	Identity and Quantity of Primary Surface Stabilizer	Identity and Quantity of Secondary Surface Stabilizer	Mean (nm)	D90 (nm)
1	5%	1% HPC-SL	0.05% DOSS	167	224
2	5%	1% HPMC	0.05% DOSS	156	215
3	5%	1% PVP	0.05% DOSS	167	226
4	5%	1% Plasdone ® S630*	0.05% DOSS	164	222
5	5%	1% HPMC	0.05% SLS	148	208

*Plasdone ® S630 (ISP) is a random copolymer of vinyl acetate and vinyl pyrrolidone.

Formulations 1–5 showed small, well-dispersed particles using the Horiba La-910 Laser Scattering Particle Size Distribution Analyzer (Horiba Instruments, Irvine, Calif.) and light microscopy. Formulations 1–5 were stable in electrolyte fluids and had acceptable physical stability at 5° C. for 4 weeks. Electrolyte fluids are representative of physiological conditions found in the human body. Formulations 1, 2, 3, and 4 also exhibited acceptable stability at 25° C. and 40° C. for 4 weeks. Formulation 5 exhibited acceptable stability at 40° C. for at least 3 weeks.

EXAMPLE 2

This example compares the pharmacokinetic parameters of nanoparticulate megestrol acetate formulations of the present invention with conventional microparticulate formulations of megestrol acetate.

Twelve male beagles, at least twelve months of age, were divided into 2 groups based on whether they were fasting or being fed. The dogs were acclimated for thirteen days prior to dosing. The animals weighed approximately 11.4 to 14.3 kg at the time of dosing, and the dose was adjusted to 10

mg/kg. Water was available ad libitum. The animals were fasted (food only) for twelve to sixteen hours prior to dosing on day 1. On day 1, each dog was administered a formulation by gavage. Following dosing, the gavage tube was flushed with 18 ml of water. In the fed study, the animals were fed a high fat meal about 1 hour prior to dosing.

The dogs were subdivided into four groups, with each group receiving either Formulation A (nanoparticulate megestrol dispersion #1, comprising 4.0% megestrol acetate, 0.8% HPMC, and 0.4% DOSS), Formulation B (nanoparticulate megestrol dispersion #2, comprising 4.0% megestrol acetate, 0.8% HPMC, and 0.04% SLS), Formulation C (suspension of microparticulate megestrol acetate, Par Pharmaceutical, Inc., New York) or Formulation D (Megace® Oral Suspension, which is a suspension of microparticulate megestrol acetate). Each formulation was adjusted to administer a dose of 10 mg/kg of megestrol acetate to the subject.

Prior to dosing, blood samples were taken from each subject. Blood samples were then collected from each subject at 15 and 30 minutes, as well as 1, 2, 3, 4, 6, 8, 24, 48, and 72 hours after dosing and centrifuged. Plasma was then separated and diluted when necessary, and subsequently analyzed for megestrol acetate by HPLC.

Tables 2 and 3 summarize the pharmacokinetic data of the four formulations administered to fasted dogs and fed dogs, respectively.

TABLE 2

Summary of Pharmacokinetic Data in Fasted Dogs

Parameters	Formulation A n = 3 (Mean ± SD)	Formulation B n = 3 (Mean ± SD)	Formulation C n = 3 (Mean ± SD)	Formulation D n = 3 (Mean ± SD)
AUC_{0-t}	37774.23 ± 11648.60	21857.68 ± 10737.53	17395.95 ± 10428.73	10094.30 ± 1990.89
AUC_{0-inf}	49408.88 ± 3392.80	27863.56 ± 15279.16	6948.48±*	12007.13 ± 1923.80
C_{max}	2209.74 ± 351.54	1563.02 ± 787.37	484.98 ± 321.70	339.92 ± 175.86
T_{max}	0.83 ± 0.29	0.50 ± 0.00	18.67 ± 9.24	2.67 ± 0.58
$t_{1/2}$	42.01 ± 33.81	30.09 ± 19.37	26.57±*	25.59 ± 7.11
K_{el}	0.025 ± 0.018	0.032 ± 0.024	0.026±*	0.028 ± 0.007

AUC_{0-t} (ng · hr/ml) = Area under the curve from time zero to the last measurable concentration;

AUC_{0-inf} (ng · hr/ml) = Area under the curve from time zero to infinity;

C_{max} (ng/ml) = Maximum plasma concentration;

T_{max} (hr) = Time to occurrence of C_{max};

$t_{1/2}$ (hr) = Apparent elimination half-life;

K_{el} (1/hr) = elimination rate constant;

*n = 1.

TABLE 3

Summary of Pharmacokinetic Data in Fed Dogs

Parameters	Formulation A n = 3 (Mean ± SD)	Formulation B n = 3 (Mean ± SD)	Formulation C n = 3 (Mean ± SD)	Formulation D n = 3 (Mean ± SD)
AUC_{0-t}	48543.56 ± 11608.55	36687.92 ± 12016.26	27332.11 ± 6488.79	31397.16 ± 5823.79
AUC_{0-inf}	61734.90 ± 4918.52	42787.74 ± 14630.92	31720.98 ± 5580.32	40218.66 ± 8649.33*
C_{max}	3777.34 ± 2489.41	2875.82 ± 1334.32	2180.73 ± 406.28	2577.83 ± 665.31
T_{max}	1.67 ± 2.02	3.00 ± 4.33	1.00 ± 0.00	0.83 ± 0.29
$T_{1/2}$	34.35 ± 12.10	26.67 ± 7.80	26.16 ± 10.88	36.60 ± 9.62*
K_{el}	0.022 ± 0.009	0.028 ± 0.010	0.31 ± 0.16	0.20 ± 0.005

AUC_{0-t} (ng · hr/ml) = Area under the curve from time zero to the last measurable concentration;

AUC_{0-inf} (ng · hr/ml) = Area under the curve from time zero to infinity;

C_{max} (ng/ml) = Maximum plasma concentration;

T_{max} (hr) = Time to occurrence of C_{max};

$T_{1/2}$ (hr) = Apparent elimination half-life;

K_{el} (1/hr) = elimination rate constant;

*n = 2.

The results in the fasted dogs show that the nanoparticulate megestrol formulations (Formulations A and B) showed dramatically superior bioavailability, as evidenced by the superior AUC and C_{max} results, as compared to the conventional microparticulate megestrol formulations (Formulations C and D). Formulation A, with a C_{max} of 2210, had a maximum concentration more than 4½ times that of Formulation C (485), and a maximum concentration more than 6½ times that of Formulation D (340). Formulation B, with a C_{max} of 1563, had a maximum concentration more than 3.2 times that of Formulation C (485), and a maximum concentration more than 4.6 times that of Formulation D (340). Also, Formulation A, with an AUC of 49,409 ng hr/mL, had an oral bioavailability more than 7 times that of Formulation C (6948 ng hr/mL) and an oral bioavailability of more than 4 times that of Formulation D (12007 ng hr/mL). Formulation B, with an AUC of 27,864 ng hr/mL, had an oral bioavailability more than 4 times that of Formulation C (6949 ng hr/mL) and an oral bioavailability more than 2 times that of Formulation D (12,007 ng hr/mL).

In addition, in the fasted dogs the nanoparticulate megestrol formulations (Formulations A and B) showed dramatically superior faster onset of action, as evidenced by the superior T_{max} results, as compared to the conventional microparticulate megestrol formulations (Formulations C and D). Formulation A, with a T_{max} of 0.83 hr, reached a maximum concentration of megestrol in less than $1/20^{th}$ the time of Formulation C (18.67 hr), and in less than $1/3^{rd}$ the time of Formulation D (2.67 hr). Formulation B, with a T_{max} of 0.50 hr, reached a maximum concentration in less than $1/37^{th}$ the time of Formulation C (18.67 hr), and in less than $1/5^{th}$ the time of Formulation D (2.67 hr).

Similarly, the results in the fed dogs show that the nanoparticulate megestrol formulations (Formulations A and B) showed dramatically superior bioavailability, as evidenced by the superior AUC and C_{max} results, as compared to the conventional microparticulate megestrol formulations (Formulations C and D). Formulation A, with a C_{max} of 3777, had a maximum concentration of about more than 1.7 times that of Formulation C (2181), and a maximum concentration of about more than 1.5 times that of Formulation D (2578). Formulation B, with a C_{max} of 2876, had a maximum concentration of about more than 1.3 times that of Formulation C (2181), and a maximum concentration of about more than 1.1 times that of Formulation D (2578). Formulation A, with an AUC of 61,735 ng hr/mL, had an oral bioavailability of more than 1.9 times that of Formulation C (31721 ng hr/mL) and more than 1.5 times that of Formulation D (40219 ng hr/mL). Formulation B, with an AUC of 42788 ng hr/mL, had an oral bioavailability of more than 1.3 times that of Formulation C (31721 ng hr/mL) and an oral bioavailability of more than 1.1 times that of Formulation D (40218 ng hr/mL).

EXAMPLE 3

This example demonstrates the physical stability of megestrol acetate dispersions at various concentrations and with the addition of sucrose, flavoring, and preservatives. Megestrol acetate was milled under high energy milling conditions using a NanoMill™2 System (Elan Drug Delivery, Inc.) in the presence of a preservative/buffer system consisting of sodium benzoate, citric acid monohydrate, and sodium citrate dihydrate. After milling, the resulting dispersion was diluted with water, sucrose, flavoring, and additional preservative/buffer to prepare dispersions containing 3% (w/w), 5% (w/w), or 9% (w/w) megestrol acetate. The resulting formulations are shown in Table 4. The physical stability of the formulations was then monitored at 25° C., 40° C., and 50° C.

TABLE 4

	Formulation Summary			
	Concentrated	Diluted, Flavored Dispersions		
API and Excipients	Nanoparticle Dispersion g/kg	Formulation E 3% Dispersion g/kg	Formulation F 5% Dispersion g/kg	Formulation G 9% Dispersion g/kg
Megestrol Acetate, USP	325.000	30.000	50.000	90.000
Hydroxypropyl Methylcellulose, USP	65.000	6.000	10.000	18.000
Docusate Sodium, USP	3.250	0.300	0.500	0.900
Sodium Benzoate, USP	1.214	1.826	1.777	1.681
Sodium Citrate Dihydrate, USP	0.910	0.091	0.089	0.084
Citric Acid Monohydrate, USP	0.061	1.369	1.333	1.260
Sucrose, USP		50.000	50.000	50.000
Natural and Artificial Lemon Flavor		0.400	0.400	0.400
Artificial Lime Flavor		0.400	0.400	0.400
Purified Water, USP	604.600	909.614	885.500	837.280

Particle size measurements (Table 5) were used to assess the physical stability. The results show almost no increase in the mean particle size at either 25° C. or 40° C., and only a slight increase in the mean particle size at 50° C. 126 days of stability measurements were obtained for the 5% and 9% dispersions and 33 days of stability were obtained for the 3% dispersion, which was prepared at a later date.

TABLE 5

	Mean particle size (nm)								
	3% Dispersion			5% Dispersion			9% Dispersion		
	25° C.	40° C.	50° C.	25° C.	40° C.	50° C.	25° C.	40° C.	50° C.
0 days	148	148	148	169	169	169	169	169	169
30 days				172	171	187	172	170	179
33 days	141	144	173						
126 days				171	174	188	168	175	182

EXAMPLE 4

The purpose of this Example was to demonstrate the improved viscosity characteristics of the dispersions of this invention.

The viscosities of three formulations of this invention (E, F, and G as described in Example 3) and two conventional commercial formulations (Formulations C and D as described in Example 2) were determined using a rheometer (model CVO-50, Bohlin Instruments). The measurements were performed at a temperature of 20° C. using a double gap (40/50) geometry.

The viscosities of the Formulations of this invention were found to be nearly Newtonian (i.e., the viscosity being independent of shear rate), and were 1.5, 2.0, and 3.5 mPa s for the 30, 50, and 90 mg/mL concentrations, respectively.

The viscosity dependence on concentration is illustrated in FIG. **1**.

The commercial formulations C and D were shear thinning in nature. Such samples cannot be characterized by a single viscosity but rather a series of viscosities measured at different shear rates. This is most conveniently illustrated as viscosity—shear rate curves as shown in FIG. **2**.

The commercial samples and the three formulations of this invention are compared in Table 6 below. Viscosities are in units of mPa s.

TABLE 6

Shear Rates of Commercial Megestrol Formulations (D and C) and the Nanoparticulate Megestrol Formulations of the Invention (E, F, & G)

	Commercial Samples		Formulations E, F, & G		
Shear Rate s^{-1}	Formulation D (mPa s)	Formulation C (mPa s)	(E) 30 mg/mL (mPa s)	(F) 50 mg/mL (mPa s)	(G) 90 mg/mL (mPa s)
0.1	4010	2860	1.5	2.0	3.5
1	929	723	"	"	"
10	215	183	"	"	"
100	49.9	46.3	"	"	"

* These samples were not measured at the 0.1 and 1 s^{-1} shear rates (the shear range was ca 2 to 100 s^{-1}) but the assessment that these exhibit Newtonian flow properties justifies the entries.

EXAMPLE 5

The purpose of this Example was to visually demonstrate the difference between the viscosity characteristics of liquid megestrol formulations of the invention as compared to conventional liquid megestrol formulations.

A sample of a 50 mg/mL nanoparticulate dispersion of megestrol acetate and two conventional commercial formulations at 40 mg/mL (Formulations C and D as described in Example 2) were each placed in a vial, which was then shaken. Attached as FIG. **3** is a photograph of the thee vials, which from left to right are the nanoparticulate megestrol acetate dispersion, Formulation C, and Formulation D.

The vial with the nanoparticulate dispersion shows a thin, silky, almost shear film coating the vial. In contrast, the vials containing the two commercial formulations show a gritty residue coating. Such a gritty residue is the same residue which coats a patient's mouth and throat upon administration. Such a coating is highly unpleasant, particularly for patients suffering from wasting (i.e., unable to eat). Thus, FIG. **3** visually demonstrates the appeal of a liquid oral nanoparticulate megestrol formulation of the invention as compared to conventional commercial liquid oral megestrol formulations.

EXAMPLE 6

The purpose of this example was to prepare nanoparticulate compositions of megestrol acetate using various surface stabilizers.

5% megestrol acetate (Par Pharmaceuticals, Inc.) was combined with 1.25% of various surface stabilizers: tyloxapol (Sterling Organics), Tween 80 (Spectrum Quality Prod-

ucts), Pluronic F-108 (BASF), Plasdone S-630 (ISP), hydroxypropylmethylcellulose (HPMC) (Shin Etsu), hydroxypropylcellulose (HPC-SL) (Nippon Soda Co., Ltd.), Kollidon K29/32 (polyvinylpyrrolidone) (ISP), or lysozyme (Fordras).

For each combination of megestrol acetate and surface stabilizer, the surface stabilizer was first dissolved in 7.875 g water for injection (WFI) (Abbott Laboratories, Inc.), followed by the addition of the milling media, PolyMill™-500 (Dow Chemical, Co.), and 0.42 g megestrol.

The slurries were charged into each of eight 18 cc NanoMill® (Elan Drug Delivery) chambers and milled for 30 min. Upon completion of milling the dispersions were harvested with a 26 gauge needle yielding the following particle sizes shown in Table 7.

All particle size distribution analyses were conducted on a Horiba LA-910 Laser Light Scattering Particle Size Distribution Analyzer (Horiba Instruments, Irvine, Calif.). RO-water was utilized as the liquid dispersing medium and a flow-through sample cell was used for all measurements. All samples were assayed in 150 cc liquid medium.

TABLE 7

Megestrol Conc.	Surface Stabilizer/Conc.	Mean Particle Size
5%	tyloxapol; 1.25%	214 nm
5%	Tween 80; 1.25%	210 nm
5%	Pluronic F-108; 1.25%	459 nm
5%	Plasdone S-630; 1.25%	292 nm
5%	HPMC; 1.25%	314 nm
5%	HPC-SL; 1.25%	623 nm
5%	PVP K29/32; 1.25%	24816 nm
5%	lysozyme; 1.25%	179 nm

The results show that tyloxapol, Tween 80, and lysozyme produced small particles without substantial aggregation. Pluronic F-108, Plasdone S-630, HPMC, HPC-SL, and K29/32 had larger particle sizes, indicating that aggregation was occurring. Thus, at the particular concentration of drug and surface stabilizer, using the described milling method, Pluronic F-108, Plasdone S-630, HPMC, HPC-SL, and K29/32 were not preferable surface stabilizers. These surface stabilizers may be useful in nanoparticulate compositions of megestrol at different drug or surface stabilizer concentrations, or when used in conjunction with another surface stabilizer.

EXAMPLE 7

The purpose of this example was to prepare nanoparticulate compositions of megestrol acetate using various surface stabilizers.

Megestrol acetate (Par Pharmaceuticals, Inc.) and various surface stabilizers, as shown in Table 8, were combined and milled, followed by determination of the particle size and stability of the resulting composition. Materials were obtained as in Example 6.

All of the samples were milled using a Dyno®-Mill (Model KDL-Series, Willy Bachofen AG, Basel, Switzerland) equipped with a 150 cc stainless steel batch chamber. Cooling water (approximate temperature 5° C.) was circulated through the mill and chamber during operation.

All particle size distribution analyses were conducted on a Horiba LA-910 Laser Light Scattering Particle Size Distribution Analyzer (Horiba Instruments, Irvine, Calif.), as described above in Example 6.

Qualitative microscopic assessments of the formulations were performed using a Leica light microscope (Type 301-371.010). Sample preparation involved diluting the product dispersions in RO-water and dispensing about 10 μL onto a glass slide. Oil immersion was utilized in conjunction with 1000× magnification.

The physical stability was assessed by storing the dispersion is 20 ml glass scintillation vials in a temperature/humidity controlled chamber at either 5° C., (25° C./60% RH), (40° C./75% RH), (50° C./75% RH), or 55° C. Samples were taken at varying time intervals and the particle size was analyzed.

For all formulations, the surface stabilizer(s) was first dissolved in WFI (Abbott Laboratories, Inc.) (75.0 g for Exp. Nos. 1, 2, 3, 7, and 8; 75.2 g for Exp. Nos. 4 and 9; 74.9 g for Exp. Nos. 5 and 6; 70.3 g for Exp. Nos. 10 and 11), followed by combining the surface stabilizer solution megestrol acetate and PolyMill™-500 polymeric grinding media. This mixture was then added to the appropriate milling chamber, milled for the time period shown in Table 8, followed by harvesting and vacuum filtering of the megestrol acetate dispersion.

TABLE 8

Exp. No.	Megestrol Conc.	Surface Stabilizer(s) and Conc.	Milling Time	Mean Particle Size	Stability
1	5%	1.25% lysozyme	20 min.	209 nm	The sample showed substantial aggregation after incubation in normal saline for 30 minutes as determined by optical microscopy.
2	5%	1.25% Tween 80	75 min.	157 nm	Upon storage at 5° C. for 15 days the sample grew to a mean diameter of 577 nm.
3	5%	1.25% tyloxapol	2 hrs.	208 nm	Optical microscopoy revealed the presence of elongated "needle-like" crystals.
4	5%	1% Pluronic F127	2 hrs.	228 nm	Upon storage at 25° C. for 5 days the sample grew to a mean diameter of 308 nm.
5	5%	1.25% HPMC 0.0625% SLS[1]	75 min.	161 nm	Upon storage at 40° C. for 19 days, the sample grew to a mean diameter of 171 nm. Incubation for 30 minutes at 40° C. in 0.01 N HCl or normal saline resulted in particle sizes of 164 nm and 209 nm, respectively.
6	5%	1.25% HPC-SL, 0.05% SLS	60 min.	167 nm	Upon storage at 40° C. for 15 days, the sample grew to a mean diameter of 194 nm. Incubation for 30 minutes at 40° C. in 0.01 N HCl or normal saline resulted in particle sizes of 183 nm and 179 nm, respectively.
7	5%	1.25% HPMC	45 min.	185 nm	Upon storage at 40° C. for 6 days, the sample grew to a mean diameter of 313 nm. Incubation for 30 minutes at 40° C in 0.01 N HCl or normal saline

TABLE 8-continued

Exp. No.	Megestrol Conc.	Surface Stabilizer(s) and Conc.	Milling Time	Mean Particle Size	Stability
					resulted in particle sizes of 2041 nm and 1826 nm, respectively. Optical microscopy revealed aggregation in both the saline and HCl samples.
8	5%	1.25% HPC-SL	45 min.	176 nm	Upon storage at 40° C. for 6 days, the sample grew to a mean diameter of 244 nm. Incubation for 30 minutes at 40° C. in 0.01 N HCl or normal saline resulted in particle sizes of 873 nm and 524 nm, respectively. Optical microscopy revealed aggregation in both the saline and HCl samples.
9	5%	1% HPMC 0.05% SLS	70 min.	152 nm	Incubation for 30 minutes at 40° C. in 0.01 N HCl or normal saline resulted in particle sizes of 155 nm and 539 nm, respectively. Optical microscopy confirmed that aggregation was present in the sample incubated in saline.
10	10%	2% HPMC 0.1% DOSS[2]	70 min.	150 nm	Following harvesting the sample was diluted to 4% API by adding WFI. Upon storage at 40° C. for 40 days, the sample had a mean diameter of 146 nm. Optical microscopy revealed small, well dispersed particles.
11	10%	2% HPMC 0.1% SLS	70 min.	146 mn	Upon storage at 40° C. for 19 days, the sample had a mean diameter of 149 nm. Optical microscopy revealed small, well dispersed particles.
12	10%	4% lysozyme	60 min.	108 nm	Upon storage at 40° C. for 9 days the sample had a mean diameter of 124 nm. Optical microscopy revealed small, well dispersed particles.

[1]Sodium lauryl sulfate (Spectrum Quality Products)
[2]Dioctyl Sodium Sulfosuccinate (Cytec)

The results shown in Table 8 indicate that the use of lysozyme (Exp. No. 1) as a surface stabilizer resulted in small well dispersed particles with a mean particle size of 209 nm, but the formulation showed aggregation when diluted into a normal saline solution. A megestrol acetate/tyloxapol sample was also stable at higher drug and stabilizer concentrations (Exp. No. 12).

Tween 80, tyloxapol, and Pluronic F127 (Exp. Nos. 2, 3, and 4) were effective primary surface stabilizers and produced well-dispersed particles without significant aggregation. Stability measurements, however, revealed rapid crystal growth for all three stabilizers. 5% megestrol acetate/1.25% Tween 80 grew from 157 nm to 577 nm after 15 days at 5° C. 5% megestrol acetate/1.25% tyloxapol showed needle-like crystals when observed under optical microscopy. 5% megestrol acetate/1.25% Pluronic F127 grew from 228 nm to 308 nm after 5 days at 25° C. Because of the rapid crystal growth observed, Tween 80, tyloxapol, and Pluronic F127 were deemed not suitable surface stabilizers at the described drug/surface stabilizer concentrations prepared under the conditions described above.

The HPC-SL formulation (Exp. No. 8) showed substantial aggregation indicating that a secondary charged stabilizer would be needed. SLS was added (Exp. No. 6) and the new formulation grew from 167 to 194 nm after storage at 40° C. for 15 days and did not show any substantial aggregation upon incubation in either 0.01N HCl or normal saline. The SLS appeared effective at preventing the aggregation but the sample showed some particle size growth.

The HPMC formulation (Exp. No. 7) showed substantial aggregation indicating that a secondary charged stabilizer would be needed. SLS was added (Exp. Nos. 5 and 11), and the new formulations showed only minimal growth from 161 nm to 171 nm (Exp. No. 5), and from 146 to 149 nm (Exp. No. 11), after storage at 40° C. for 19 days. In addition, the composition of Exp. No. 5 did not show any substantial aggregation upon incubation in either 0.01N HCl or normal saline. The SLS was effective at preventing the aggregation without causing significant crystal growth.

An attempt was made to reduce the concentration of the primary and secondary stabilizers (Exp. No. 9) and resulted in a post-milling mean diameter of 152 nm. Incubation for 30 minutes at 40° C. in normal saline resulted in particle sizes of 539 nm. Optical microscopy confirmed that aggregation was present in the sample incubated in saline.

Docusate sodium (DOSS) was tried as a secondary stabilizer (Exp. No. 10) and resulted in well-dispersed particles with a mean diameter of 150 nm. Upon storage at 40° C. for 40 days, the sample had a mean diameter of 146 nm. Optical microscopy revealed small, well-dispersed particles. DOSS seemed to result in even less particle size growth than SLS.

EXAMPLE 8

The purpose of this example was to prepare nanoparticulate compositions of megestrol acetate using various surface stabilizers and further including preservatives or excipients.

The materials and methods were the same as in Example 7, except that for several of the examples different sources of megestrol acetate were used (See Table 9). In addition, for Exp. Nos. 5, a NanoMill® milling system (Elan Drug Delivery) was used. Several different combinations of megestrol acetate, surface stabilizer(s), and one or more preservatives or excipients were prepared, following by testing the compositions for particle size and stability.

The surface stabilizer(s) and one or more preservatives were first dissolved in WFI, followed by combining the solution with megestrol acetate and the grinding media. This mixture was then added to the milling chamber and milled for the time period set forth in Table 9, below.

For several of the experiments, following milling the megestrol acetate dispersion was combined with a flavored suspension. The stability of the resultant composition was then evaluated.

The formulation details and results are shown in Table 9, below.

TABLE 9

Exp.	Megestrol Conc.	Surface Stabilizer(s) and Conc.	Preservatives/Excipients	Milling Time	Mean Particle Size	Stability
1	10%	2% HPMC 0.1% DOSS	Sodium Benzoate (0.4 g), Sodium Citrate Dihydrate (20 mg) Citric Acid Monohydrate (0.3 g)	75 min	146 nm	After milling a flavored suspension was prepared by adding sucrose (2.5 g), xanthan gum (0.113 g), glycerol (13.75 g), lemon flavor (0.1 g), WFI (18.6 g), and 20.0 g of the milled dispersion. Upon storage at 40° C. for 24 days, the sample showed aggregation with a mean diameter of 837 nm. Incubation for 30 minutes at 40° C. in 0.01 N HCl or normal saline resulted in particle sizes of 206 nm and 3425 nm, respectively. Optical microscopy confirmed that the sample incubated in saline had aggregated.
2	25%	5% HPMC 0.05% DOSS	Sodium Benzoate (0.11 g) Citric Acid Monohydrate (0.08 g)	95 min.	See right column.	16 g of the milled drug dispersion was combined with sucrose (5 g), lime flavor (80 mg), and WFI (78.9 g). The diluted drug dispersion had a mean diameter of 192. After 6 days at 55° C. the particles had a mean diameter of 10 microns, indicating substantial aggregation
3	25%	5% HPMC, 0.15% DOSS	Sodium Benzoate (0.11 g) Citric Acid Monohydrate (0.08 g)	95 min.	See right column.	16 g of the milled drug dispersion was combined with sucrose (5 g), lime flavor (80 mg), and WFI (78.9 g). The diluted drug dispersion had a mean diameter of 173 nm. After 12 days at 55° C. the particles had a mean diameter of 295 nm.
4	32.5%1	6.5% HPMC 0.33% DOSS	Sodium Benzoate (13.07 g) Sodium Citrate Dihydrate (0.65 g) Citric Acid Monohydrate (9.8 g)	15.5 hrs	160 nm	Upon storage at 50° C. for 44 days, the mean diameter was 190 nm.
5	32.5%	6.5% HPMC 0.33% DOSS	Sodium Benzoate (9.71 g) Sodium Citrate Dihydrate (0.49 g) Citric Acid Monohydrate (7.28 g)	12 hrs	147 nm	Upon storage at 50° C. for 44 days the mean diameter was 178 nm.

[1]Pharmacia
[2]Pharmabios

In Exp. No. 1 of Table 9, a sweetened, flavored dispersion was prepared by mimicking the current commercial formulation of megestrol acetate that contains sucrose, xanthan gum, glycerol, lemon and lime flavors, and is preserved and buffered with sodium benzoate and citric acid. Upon storage at 40° C. for 24 days the sample showed aggregation with a mean diameter of 837 nm. Incubation for 30 minutes at 40° C. in 0.01N HCl or normal saline resulted in particle sizes of 206 nm and 3425 nm, respectively. Optical microscopy confirmed that the sample incubated in saline had aggregated. The aggregation upon storage indicated that this particular combination of drug and surface stabilizer, at the concentrations used and methodology employed to make the compositions, would not be an effective formulation.

For Exp. Nos. 4 and 5, the formulation was scaled-up in a NanoMill™-2 system to determine if the scale-up would effect the physical stability. Two different sources of megestrol acetate were tested: Pharmacia and Pharmabios. The product of Exp. No. 4 had a mean diameter of 160 nm without ultrasound. Upon storage at 50° C. for 44 days the mean diameter was 190 nm. The composition of Exp. No. 5 had a post-milling mean diameter of 147 nm without ultrasound. Upon storage at 50° C. for 44 days the mean diameter was 178 nm. Both sources of active agent milled effectively and showed little particle size growth even at 50° C.

The results of Examples 6 and 7 showed that high energy milling with polymeric attrition media could be used to produce stable nanoparticulate colloidal dispersions of megestrol acetate suitable for oral administration to animals or humans. The primary stabilizer HPMC required the presence of DOSS or SLS to prevent aggregation at the concentrations of drug and stabilizer tested (other combinations of drug and HPMC concentrations may result in a stable composition without the addition of a second surface stabilizer). In general, average particle sizes of less than about 160 nm could be obtained. Tests conducted with two sources of megestrol acetate revealed that both sources milled effectively and exhibited excellent physical stability.

Based on mean particle size, physical stability, and the pre-clinical dog study, the best nanoparticulate megestrol acetate formulation for commercial development, based on the results of the data given in the examples, consisted of 32.5% megestrol acetate, 6.5% HPMC, and 0.325% DOSS (i.e., a drug:HPMC ratio of 1:5 and a drug:DOSS ratio of 1:100. The formulation milled effectively in the presence of preserved water (0.2% sodium benzoate, 0.01% sodium citrate dihydrate, and 0.15% citric acid monohydrate). Upon dilution with preserved water, flavors, and sucrose none of the dispersions showed severe aggregation, except for the dispersions containing xanthan gum (data not shown) or low levels of DOSS. The alcohol-based flavors did not effect the physical stability nor did several freeze-thaw cycles (data not shown).

EXAMPLE 9

This example compares the pharmacokinetic parameters of nanoparticulate megestrol acetate formulations of the invention with a conventional microparticulate formulation of megestrol acetate. Results were obtained from a fasted study group consisting of 36 male subjects, 18 years of age or older. For a fed study group, results from 32 subjects were analyzed.

Subjects in the fasted study group and the fed study group were administered study drugs in four successive periods. Treatment A (1×150 mg drug as 5 ml of a 3% megestrol acetate nanoparticulate formulation) was administered in the first period. Reference Treatment B (1×800 mg drug as 20

ml of a 4% megestrol acetate Megace® Oral Suspension) was administered in the second period. Treatment C (1×250 mg drug as 5 ml of a 5% megestrol acetate nanoparticulate formulation) was administered in the third period. Treatment D (1×450 mg drug as 5 ml of a 9% megestrol acetate nanoparticulate formulation) was administered in the fourth period. The formulations of Treatments A, C, and D are listed in Table 10 below, with particle size information (microns) provided in Table 11.

In each period, subjects were confined from at least 10 hours prior to drug administration to after the last sample collection. In the fasted study group, no food was consumed from at least 10 hours before dosing to at least 4 hours after dosing. In the fed study group, a high-calorie breakfast (containing about 800 to 1000 calories, approximately 50% of which were from fat) was served within 30 minutes prior to dosing; dosing occurred within 5 minutes after the breakfast was completed. A controlled meal was served to both groups after 4 hours after dosing, and standard meals were served at appropriate times thereafter. The meals in all four periods were identical. Subjects in the fasted study group were not allowed fluid intake from 1 hour before dosing to 1 hour after. Subjects in the fed study group were also not allowed fluid intake during this period except for fluids provided with the high-calorie breakfast. Water was provided ad libitum to both study groups at all other times.

Blood samples were obtained before dosing, at half-hourly intervals in the 6 hours following dosing, and at 7, 8, 12, 16, 20, 24, 36, 48, 72, and 96 hours after dosing. Megestrol acetate in plasma samples was then determined.

Table 12 below summarizes pharmacokinetic data for the fasted study group, and Table 13 below summarizes pharmacokinetic data for the fed study group.

Treatments A, C, and D in fasting subjects produced dose-normalized values for AUC_{0-t} and AUC_{0-inf} that were approximately twice those of Reference Treatment B. Maximum dose-normalized megestrol acetate concentrations in Treatments A, C, and D were approximately 9 to 12 times that of Reference Treatment B. The maximum megestrol acetate concentration for the 150 mg-dose of Treatment A was approximately twice that of the 800 mg-dose of reference Treatment B. Moreover, comparable values of AUC_{0-t} and AUC_{0-inf} were observed for the 450 mg-dose of Treatment D and the 800 mg-dose of Reference Treatment B.

Treatments A, C, and D in fed subjects produced dose-normalized values for AUC_{0-t} and AUC_{0-inf} that were approximately 8 to 10% greater than those of Reference Treatment B. Maximum dose-normalized megestrol acetate concentrations in Treatments A, C, and D were approximately 38 to 46% greater than that of Reference Treatment B. Megestrol acetate onset for Treatments A, C, and D was comparable to Reference Treatment B.

Nanoparticulate megestrol acetate formulations, therefore, exhibited superior oral bioavailability, relative to the Megace® Oral Suspension, in fasting and fed human subjects.

TABLE 10

Formulations for Megestrol Acetate Oral Suspension 3, 5% and 9%

	Strengths		
Ingredients	3% w/w (30 mg/mL)	5% w/w (50 mg/mL)	9% w/w (90 mg/mL)
Megestrol Acetate	3.000	5.000	9.000
Hydroxypropyl Methylcellulose	0.600	1.000	1.800
Docusate Sodium	0.030	0.050	0.090
Sodium Benzoate	0.183	0.178	0.168
Sodium Citrate Dihydrate	0.009	0.009	0.008
Citric Acid Monohydrate	0.137	0.133	0.126
Sucrose	5.000	5.000	5.000
Natural and Artificial Lemon Flavor	0.040	0.040	0.040
Artificial Lime Flavor	0.040	0.040	0.040
Purified Water	90.961	88.550	83.727
TOTAL	100.000	100.000	100.000

TABLE 11

Particle Size Data for the Megestrol Acetate Oral Suspensions*

	Strength 30 mg/g			Strength 50 mg/g			Strength 90 mg/g		
	d(0.1)	d(0.5)	d(0.9)	d(0.1)	d(0.5)	d(0.9)	d(0.1)	d(0.5)	d(0.9)
Initial	0.068	0.123	0.223	0.069	0.125	0.229	0.068	0.124	0.227
ACC/1 month	0.070	0.129	0.237	0.070	0.127	0.231	0.070	0.127	0.230
ACC/2 months	0.070	0.127	0.231	0.070	0.127	0.233	0.073	0.126	0.221
ACC/3 months	0.070	0.129	0.237	0.070	0.128	0.235	0.070	0.128	0.234

TABLE 11-continued

Particle Size Data for the Megestrol Acetate Oral Suspensions*

	Strength 30 mg/g			Strength 50 mg/g			Strength 90 mg/g		
	d(0.1)	d(0.5)	d(0.9)	d(0.1)	d(0.5)	d(0.9)	d(0.1)	d(0.5)	d(0.9)
Initial	0.068	0.123	0.223	0.069	0.125	0.229	0.068	0.124	0.227
RT 3 months	0.070	0.128	0.237	0.073	0.128	0.224	0.067	0.121	0.223

*All particle sizes are given in microns. "d(0.1)" means distribution of smallest 10% of the particles, i.e., d(0.1) 10 μm means 10% of the particles are less than 10%. Similarly, "d(0.5)" means distribution of the smallest 50% of the particles, and "d(0.9)" means distribution of the smallest 90% of the particles. Thus, d(0.9) means that 90% of the particles are less than XX μm.

TABLE 12

Summary of Pharmacokinetic Data in Fasted Human Subjects*

Parameters	Treatment A (Mean ± SD)	Ref. Treatment B (Mean ± SD)	Treatment C (Mean ± SD)	Treatment D (Mean ± SD)
AUC_{0-t}	2800 ± 900	7000 ± 5000	4700 ± 1800	8500 ± 3200
AUC_{0-inf}	3100 ± 1000	9000 ± 9000	5200 ± 2100	9000 ± 4000
C_{max}	410 ± 120	190 ± 110	650 ± 200	950 ± 270
T_{max}	1.7 ± 0.9	6 ± 6	1.6 ± 1.0	1.7 ± 1.1
$t_{1/2}$	35 ± 13	31 ± 19	34 ± 10	34 ± 12
K_{el}	0.023 ± 0.011	0.026 ± 0.009	0.022 ± 0.008	0.023 ± 0.008

AUC_{0-t} (ng · hr/ml) = Area under the curve from time zero to the last measurable concentration;
AUC_{0-inf} (ng · hr/ml) = Area under the curve from time zero to infinity;
C_{max} (ng/ml) = Maximum plasma concentration;
T_{max} (hr) = Time to occurrence of C_{max};
$t_{1/2}$ (hr) = Apparent elimination half-life;
K_{el} (1/hr) = Elimination rate constant;
*n = 36.

TABLE 13

Summary of Pharmacokinetic Data in Fed Human Subjects*

Parameters	Treatment A (Mean ± SD)	Ref. Treatment B (Mean ± SD)	Treatment C (Mean ± SD)	Treatment D (Mean ± SD)
AUC_{0-t}	3500 ± 1100	17000 ± 5000	5700 ± 1600	10500 ± 3000
AUC_{0-inf}	3900 ± 1300	19000 ± 6000	6300 ± 2000	12000 ± 4000
C_{max}	380 ± 140	1400 ± 400	590 ± 170	1080 ± 290
T_{max}	3.8 ± 3.5	3.9 ± 0.9	3.4 ± 1.7	3.2 ± 1.7
$t_{1/2}$	35 ± 12	33 ± 9	35 ± 10	38 ± 12
K_{el}	0.023 ± 0.013	0.023 ± 0.007	0.023 ± 0.009	0.021 ± 0.008

AUC_{0-t} (ng · hr/ml) = Area under the curve from time zero to the last measurable concentration;
AUC_{0-inf} (ng · hr/ml) = Area under the curve from time zero to infinity;
C_{max} (ng/ml) = Maximum plasma concentration;
T_{max} (hr) = Time to occurrence of C_{max};
$t_{1/2}$ (hr) = Apparent elimination half-life;
K_{el} (1/hr) = Elimination rate constant;
*n = 32.

It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

We claim:

1. A method of increasing the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass, comprising administering to the human patient a megestrol formulation, wherein:

(a) the megestrol acetate formulation is a dose of about 40 mg to about 800 mg in about a 5 mL dose of an oral suspension;

(b) the megestrol acetate formulation comprises megestrol particles having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer associated with the surface of the megestrol particles; and

(c) the administration is once daily;

wherein after a single administration in a human subject of the formulation there is no substantial differ-

ence in the C_{max} of megestrol when the formulation is administered to the subject in a fed versus a fasted state,

wherein fasted state is defined as the subject having no food within at least the previous 10 hours, and wherein fed state is defined as the subject having a high-calorie meal within approximately 30 minutes of dosing.

2. The method of claim **1**, wherein the anorexia, cachexia or loss of body mass is associated with a diagnosis of HIV or AIDS in the human patient.

3. The method of claim **1**, wherein the anorexia, cachexia or loss of body mass is associated with a diagnosis of cancer in the human patient.

4. A method of increasing the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass, comprising administering to the human patient a megestrol formulation, wherein:

(a) the megestrol acetate formulation is a dose of about 40 mg to about 800 mg in about a 5 mL dose of an oral suspension;

(b) the megestrol acetate formulation comprises megestrol particles having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer associated with the surface of the megestrol particles; and

(c) the administration is once daily;

wherein after a single administration in a human subject of the formulation the difference in the C_{max} of the megestrol when administered in a fed versus a fasted state is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%, wherein fasted state is defined as the subject having no food within at least the previous 10 hours, and wherein fed state is defined as the subject having a high-calorie meal within approximately 30 minutes of dosing.

5. The method of claim **4**, wherein the difference in C_{max} is less than about 60%.

6. The method of claim **1**, wherein there is a difference in the mean T_{max} for the nanoparticulate megestrol composition when administered in fed versus fasted states, and that difference is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

7. The method of claim **1**, wherein formulation exhibits a mean C_{max} selected from the group consisting of greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130% greater than about 140%, and greater than about 150%, than the mean C_{max} exhibited by a standard commercial, non-nanoparticulate composition of megestrol, administered at the same dosage.

8. The method of claim **1**, wherein there is a difference in absorption (AUC) when the composition is administered in fed versus fasted states, and the difference is selected from the group consisting of less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

9. The method of claim **1**, wherein the anorexia, cachexia or loss of body mass is associated with cancer.

10. The method of claim **1**, wherein the anorexia, cachexia or loss of body mass is associated with HIV or AIDS.

11. The method of claim **1**, wherein a maximum blood plasma concentration of megestrol is attained in about 1 hour or less after administration of the megestrol formulation in fasting subjects.

12. The method of claim **1**, wherein a maximum blood plasma concentration of megestrol of at least about 700 ng/ml is obtained.

13. The method of claim **12**, wherein the maximum blood plasma concentration of megestrol is at least about 700 ng/ml and is attained in less than 5 hours after administration of the megestrol formulation.

14. The method of claim **1**, wherein the maximum blood plasma concentration of megestrol is at least about 400 ng/ml and is attained in less than 5 hours after administration of the megestrol formulation.

15. The method of claim **1**, wherein a mean C_{max} of about 300 ng/ml to about 2000 ng/ml is obtained after a single administration of the formulation in the human subject in a fasted state.

16. The method of claim **1**, wherein the surface stabilizer is selected from the group consisting of nonionic, cationic, ionic, and zwitterionic surfactants.

17. The method of claim **1**, wherein the surface stabilizer is selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin, dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers, poloxamines, Tetronic 1508, (tetrafunctional block copolymer derived from the addition of propylene oxide and ethylene oxide to ethylenediamine having an average molecular weight of 30,000) alkyl aryl polyether sulfonate, mixture of sucrose stearate and sucrose distearate, p-isononylphenoxy-poly-(glycidol), $C_{18}H_{37}CH_2(CON(CH_3)—CH_2(CHOH)_4(CH_2OH)_2$, decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, poly-n-methylpyridinium, anthryul pyridinium chloride, chitosan, polyl-

ysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide, hexyldesyltrimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, stearyltrimethylammonium chloride, benzyldi(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15} dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylaluminum bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts, alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, vinyl pyridine, lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, alkylimidazolium salt, imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, and cationic guar.

18. The method of claim **4**, wherein there is a difference in the mean T_{max} for the nanoparticulate megestrol composition when administered in fed versus fasted states, and that difference is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

19. The method of claim **4**, wherein the formulation exhibits a mean C_{max} selected from the group consisting of greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, and greater than about 150%, than the mean C_{max} exhibited by a standard commercial, non-nanoparticulate composition of megestrol, administered at the same dosage.

20. The method of claim **1**, wherein there is a difference in absorption (AUC) when the composition is administered in fed versus fasted states, and the difference is selected from the group consisting of less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

21. The method of claim **4**, wherein the anorexia, cachexia or loss of body mass is associated with a diagnosis of HIV or AIDS in the human patient.

22. The method of claim **4**, wherein the anorexia, cachexia or loss of body mass is associated with a diagnosis of cancer in the human patient.

23. The method of claim **4**, wherein the anorexia, cachexia or loss of body mass is associated with cancer.

24. The method of claim **4**, wherein the anorexia, cachexia or loss of body mass is associated with HIV or AIDS.

25. The method of claim **4**, wherein a maximum blood plasma concentration of megestrol is attained in about 1 hour or less after administration of the megestrol formulation in fasting subjects.

26. The method of claim **4**, wherein a maximum blood plasma concentration of megestrol of at least about 700 ng/ml is obtained.

27. The method of claim **26**, wherein the maximum blood plasma concentration of megestrol is at least about 700 ng/ml and is attained in less than 5 hours after administration of the megestrol formulation.

28. The method of claim **4**, wherein the maximum blood plasma concentration of megestrol is at least about 400 ng/ml and is attained in less than 5 hours after administration of the megestrol formulation.

29. The method of claim **4**, wherein a mean C_{max} of about 300 ng/ml to about 2000 ng/ml is obtained after a single administration of the formulation in the human subject in a fasted state.

30. The method of claim **4**, wherein the surface stabilizer is selected from the group consisting of nonionic, cationic, ionic, and zwitterionic surfactants.

31. The method of claim **4**, wherein the surface stabilizer is selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin, dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers, poloxamines, Tetronic 1508, alkyl aryl polyether sulfonate, mixture of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), $C_{18}H_{37}CH_2(CON(CH_3)—CH_2(CHOH)_4(CH_2OH)_2$, decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-

D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, poly-n-methylpyridinium, anthryul pyridinium chloride, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide, hexyldesyltrimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15} dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl $(ethenoxy)_4$ ammonium chloride or bromide, N-alkyl (C_{12-18}) dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts, alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, vinyl pyridine, lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, alkylimidazolium salt, imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, and cationic guar.

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35 U.S.C. § 103

United States Code
Title 35. Patents
Part II. Patentability of Inventions and Grant of Patents
Chapter 10. Patentability of Inventions

§ 103. Conditions for patentability; non-obvious subject matter

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.